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TRENDS IN THERAPEUTIC RESEARCH

*(Presidential Address)**

ARTHUR C. DEGRAFF, M.D.†

New York, N. Y.

In its fifty-nine years of existence, the American Therapeutic Society has been the only medical society stressing therapeutics, and over the course of years the papers presented at our meetings have reflected the trends in therapy. The future of this Society is tied up with the future of therapeutic research and our course will depend on how well we as members today are able to discern these trends. As your President this year, it seems fitting to review some of the important changes in therapy since the founding of the Society and then attempt to make a projection into the future.

At the turn of the century, great changes were taking place in medical education. The old proprietary medical schools were making way for the scientific medical colleges as we know them today. Many medical colleges became part of a university. The faculty members were encouraged to carry on research as well as teaching. Subjects such as physiology, biochemistry, pharmacology and immunology found their places alongside anatomy, pathology and clinical subjects. The students were taught more by actual contact with patients than by lectures as formerly. Experimental methods of the laboratory were beginning to be applied to the clinic. Progress, however, was slow. Therapy in those days was largely an art, not a science, and the physician had to conceal his inadequacies by such devices as writing his prescription in Latin. Even as late as 1917, the physician had little to offer in the way of medical treatment. Surgery, however, had made great strides, and the surgeon in those days was often the most important member of a medical group. Medical specialities existed largely for diagnosis, not treatment. The pneumonia specialist could not prevent the high mortality in older patients; the diabetic specialist had only diet to use in therapy. The young diabetic, particularly, led a miserable existence in those days. The heart specialist had available digitalis and nitroglycerin as the only really good drugs for his cardiac patient. Tuberculosis was treated by long-term sanitarium care.

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† Address: 850 Park Avenue, New York, N. Y.

Some brilliant advances were due to lucky breakthroughs, such as the discovery of insulin by Banting and Best, and of penicillin by Fleming. By and large, however, the major advances in therapy were due to a scientific development over a broad front. Once the biochemists had worked out accurate microchemical methods, functions of organs such as the adrenal gland began to be understood more clearly. Specific chemical substances were isolated from organs and tissues, and the roles of these chemical substances in life processes was determined. The physiologist, who formerly dealt almost entirely with mechanical problems, became more concerned with biochemistry, so that at the present time it is often impossible to distinguish a physiologist from a biochemist. The pharmacologist, who was once defined by Lombard as "one who recorded the blood pressure on a smoked drum after injecting a drug into an animal," is now applying biochemical and physiological techniques to his science. So, today, pharmacology by its broad coverage can truly be defined as a science which deals with the action of drugs on living things. It has been the development of modern pharmacology which has made the therapeutics of today a scientific discipline. At the present time pharmacology is important in many branches of therapy. For instance, pharmacological knowledge of anesthetics, preoperative medications and antiarrhythmic drugs has helped considerably to lower operative mortality.

Our advances, then, have been due to scientific methods applied to therapeutics. The management of a patient with advanced congestive heart failure might be regarded superficially as an art. Actually, the physician who does the best job is one who has accurate basic knowledge of electrolyte and water balance and how this balance is affected not only by congestive heart failure but by the very drugs he is using in treatment. This is also true in other fields of therapeutics. The treatment of a patient is no longer carried out by rule of thumb, but by making use of a great deal of scientific information.

THE MECHANICS BY WHICH THERAPY HAS CHANGED FROM AN ART TO A SCIENCE

1. *A change in philosophy.* In the days of therapeutic nihilism, study of morphology was considered extremely important. The bright young men in medicine, anxious for advancement, did their graduate work in pathology. Shortly after World War I and in the early 1920's a change took place, in that the clinician of the future took his basic training in physiology. Many who started in physiology went on into pharmacology to obtain better preparation for understanding the use of drugs in patients. In the course of several years the clinicians trained in physiological and pharmacological research methods were able to apply these techniques to clinical problems and also to develop special techniques suited particularly for evaluation of therapy in patients.

2. *Increased funds for research.* Very few research fellowships were available in the 1920's. Now there are so many research fellowships that it is often difficult to find the right persons to fill them. Also, money is available from many different sources to provide the necessary material for research. Many of our medical schools today could not continue operating if it were not for the large number of grants-in-aid made to them each year. The public is now research-minded;

witness the large sums made available for this purpose by such organizations as the American Heart Association and the American Cancer Society. It should be pointed out that the American Heart Association has led the way for other health organizations in budgeting a substantial portion of its annual income for research. Previously, organizations of a similar type, such as the National Tuberculosis Association and the Infantile Paralysis group, spent their money largely for patient care or public education. The government, particularly through the United States Public Health Service, is allocating huge sums of money for medical research, a considerable amount of which has therapeutic implications.

3. *The pharmaceutical industry.* It is only in the past twenty years or so that the pharmaceutical industry has become interested in research. It has learned that research is really good business. Very fine research laboratories have been built in recent years by all of the outstanding ethical drug companies. In these laboratories investigators develop new drugs and carry on extensive pharmacological testing and screening. With this type of work largely taken over by the pharmaceutical industry, it is possible for university workers to spend more time on basic research problems. However, the drug industry must depend on the well trained clinician to determine whether or not a new drug is really of any value in the patient. Therefore, drug companies allocate considerable sums of money to support research in various hospitals and medical centers. These research grants from the drug houses have helped materially to improve the quality of clinical research studies.

4. *Governmental regulations.* In 1939, the Food, Drug and Cosmetics Act was passed. In this act, conditions are described as to how new drugs can be introduced. A new application is required for each new drug. Proof must be submitted that the drug is safe, and its area of therapeutic value must be defined. In order to get this information, the drug company must have clinical studies which are well controlled. These clinical studies must be performed in the hospital by competent clinicians. Thus the government indirectly, through the Food and Drug Administration, is a potent agent in stimulating good clinical therapeutic research.

5. *The use of statistical methods.* These methods have been particularly valuable in therapeutic research when the crucial experiment is rarely available. Mainland has stated, "Clinical experimentation, an extremely difficult field, seems to have shown more progress than pure laboratory research, especially in complex cooperative research involving well designed plans." He cites the classic study of the British Medical Research Council on streptomycin in pulmonary tuberculosis. In this country, the Irvington House five-year study to evaluate various types of antibiotic prophylaxis in rheumatic fever is an excellent example of well planned clinical research using statistical methods. Perhaps one of the most fertile fields for use of statistics is in the evaluation of drugs for symptomatic relief—for example, the sedatives, tranquilizers, antihistaminics and antispasmodics. Not only must there be randomization in order to avoid bias, but there must be selection of truly representative groups in order to warrant general conclusions. It should be emphasized that in many hospitals patients are not representative of the population as a whole. The basic data must be sound; otherwise, statistical

methods will be of no help. The work must be planned in advance. Mainland points out that in medical research we often think that a test of statistical significance is the end of the road, *i.e.*, that something statistically "significant" must be important. He illustrates this point by an example which is quite topical. "In a group of men there may be a highly significant association between the level of a certain blood lipid and the subsequent occurrence of coronary heart disease; but if the level of this lipid is used to predict coronary disease and fails to do so in 30% of the men who develop the disease, the lipid can hardly be described as a useful indicator in the individual man." Any physician who is himself not a well trained statistician should plan his clinical research study in cooperation with a statistician from the very beginning and should have that statistician's help and guidance throughout the progress of the study until the manuscript describing the work is ready for publication. If this is not done, the physician may waste a great deal of time and effort in fruitless research.

GENERAL TRENDS

1. Fundamental research will be made at cell level (cell membrane, the nucleus, intracellular fluid). Enzymatic action is being studied in small groups of cells and even in the individual cell. This type of research will yield basic knowledge as to the precise action of drugs.

2. Biophysical studies will be more extensive. The closer the research worker gets to discovering what is going on in the individual cell and how drugs affect it, the greater will be the role of physical measurements in research. Not only will we be concerned with the passage of ions and particles, but also with the principles of quantitative physics and thermodynamics. Radioactive materials will be used in greater degree. At present, only the surface has been scratched in the use of radioactive substances in pharmacological research.

3. With the development of new drugs becoming almost entirely the problem of the research department of pharmaceutical houses, therapeutic studies in hospitals will become better controlled, and use will be made of statistical methods when necessary. The uncontrolled clinical study will, we hope, be a thing of the past.

4. More therapeutic research will be conducted on problems of chronic disease and old age. These studies will be closely correlated with physiological and biochemical data. More and more effort in research will be directed towards the determination of means by which the host builds up resistance to disease. The goal will be to make the body so resistant to disease that therapy will not be necessary.

5. Psychotherapeutic investigation will turn towards biochemical studies. It is possible that certain psychiatric states may be treated effectively with drugs.

One can expect steady progress over many fronts. In what area a sudden breakthrough may occur or when it will occur cannot be predicted. It is like a war: the continuous, relentless pursuit of the enemy will eventually win a war, but no general cares to predict where any individual battle will be fought and what may be gained from that particular battle.

Although we have reason to believe that great advances will be made in therapeutics in the coming years, and therefore the trend is excellent, certain undesirable features in the research field today have become evident. Unless controlled, they may eventually stifle true progress. I should like to spend a few moments discussing some of these undesirable trends.

1. Dearth of qualified workers. As more research jobs become available, it will become increasingly difficult to fill these jobs with honest, hard-working, sincere investigators who have an intense curiosity and zeal for discovery. Second and third raters will get jobs which to them mean nothing but security. A true research worker is a dedicated one. In the early 1920's there were very few research jobs, the salaries were low, the facilities were not too good, and there was no glamour. Only the person who possessed the true spirit of research took such a job. In those days technical equipment for a particular project was often unavailable, and the research worker had to be ingenious enough to assemble or even build his own equipment. Such an investigator put in long hours, working from early morning till late at night, including week-ends and holidays. He had no secretary. He typed his paper on his own portable typewriter and paid his own expenses to deliver the paper at a medical meeting. Contrast this man with some of our so-called research workers today. I am sure you have at least one of the type I am about to describe in your medical school. He is the pampered darling. He cannot do research without the newest and most expensive equipment, which is operated by technicians. He has a secretary to do his typing and occasionally even to ghost-write his papers. He never arrives at the laboratory before 9:30 a.m., and he leaves before 5:00 p.m. His expenses to medical meetings are all paid for him, so that he can deliver a mediocre paper. Fortunately, as yet, this type of person is not too common. Unfortunately, however, even though his research effort is poor his political ability is often excellent, so that he can maneuver himself into a position of authority where he can stifle the research work of others.

2. Too much government control. No matter how much care is taken to avoid interference by politicians, the politicians still must vote the appropriation for the budget. If the pickings look good enough to them, they will eventually intrude. Only a few years ago a Senator almost succeeded in having a quack cancer cure used in Veterans hospitals throughout the country. At the present time governmental agencies such as the Food and Drug Administration and the National Institutes of Health are doing an excellent job. I hope sincerely that they will continue to do so and not be hamstrung by politicians.

3. Overzealous sales departments of pharmaceutical houses. By and large, the pharmaceutical industry has done an excellent job in the furtherance of therapeutic research. However, largely through pressure from the sales department, drug houses have produced an endless succession of drug combinations with a new name coined for each combination. In many instances, the sole purpose appears to be to increase profits, as there is no particular merit in the combination. The physician of fifty years ago wrote prescriptions containing many ingredients. Much time was spent in medical schools in the teaching of prescription writing and incompatibilities. In the 1920's the old polypharmacy

gave way to single-drug prescriptions. This was a real advance in therapeutics, because no two drugs have the same rates of absorption or duration of action. It is only on rare occasions that a combination of two drugs is to be preferred over the same drugs given singly. Now the sales departments of the drug houses have reverted to polypharmacy of a particularly vicious form, in that the new names coined for the combinations make it appear to the physician that he is using a new drug. Combinations of two, three, and sometimes even five or six drugs are advertised. Reserpine, for instance, is combined with phenobarbital, with an antihistaminic, and with one or more other hypotensive agents—each combination under a different name. In such a combination it is impossible for the physician to grade the dosage of each drug to suit his patient. A more serious feature is the greater chance of drug reactions. Dermatologists tell me that the commonest skin lesions now seen are those due to drugs. In all fairness it should be stated that the doctors themselves are also at fault. If doctors did not prescribe these combinations of drugs, there would be no sale for them and the drug companies would stop producing them.

Further to confuse the doctors, the same drug may have many different names; for instance, erythromycin, tetracyclin, and digitoxin are marketed under several pseudonyms. Why should a company which for many years has been selling digoxin as digoxin suddenly change the name to Lanoxin? Is this a sales promotion scheme to confuse the physician into thinking that a new cardiac glycoside is available, replacing digoxin? Such shenanigans are certainly not the sort of thing that the medical profession should expect from a highly respected ethical drug firm. Let us hope this trend will not continue and that in the future the hucksters in the pharmaceutical houses will be booted out, so that the medical director and the research department will again be in the saddle to permit orderly development and sale of increasingly useful therapeutic agents.

It should be said that the medical departments of many pharmaceutical firms have done an excellent service to physicians in distributing medical information in well illustrated brochures and pamphlets. This is a refreshing contrast to the gaudy cards and promotional literature which clutter up the doctor's mail and waste the time of his secretary.

How can our Society act to be a power and influence in therapeutics in the future? There are many positive things we can do. We should continue to be the one Society that is devoted exclusively to therapeutics. It is in our Society that new therapy in every field is described and discussed thoroughly at our meetings. It is to our Society that the medical profession should come to find out what is the best as well as the newest in therapy. To do this, we should:

1. Take into our membership those who are actively engaged in therapeutic research. That means young research workers. Although it is desirable many times to invite speakers for our programs, the goal should be to have such an active group of young research workers as members that the bulk of the papers come from the membership.

2. Have some mechanism by which the Society is constantly aware of what is going on in therapeutic research throughout the country. In that way we shall

be able to get material on our programs before the work is published. This does not rule out the re-evaluation of some form of therapy by a symposium or panel discussion when such seems necessary and desirable. One method which will help materially to accomplish this goal is to have a standing committee, some members of which are in medical schools and others in the pharmaceutical industry.

3. Be a positive force through special committees and other means to encourage good therapeutic research. An excellent step in this direction was taken last year when it was voted to offer a prize for the best paper on original research in therapeutics, the author of which was to have all expenses paid to the meeting to present his paper. Eventually stimuli of this sort should lead to a flood of good abstract papers, from which the best can be chosen for presentation at our annual meeting.

4. Be a positive force to improve therapy throughout the country. For instance, the Society might have a committee whose purpose is to assist hospital medical staffs to set up good drug and formulary committees. The Bellevue Hospital Drugs and Formulary Committee in New York City, now in operation over twenty years in its present form, has been able not only to promote good therapy but to save the hospital thousands of dollars a year by preventing needless duplication and senseless combinations of drugs.

5. Be of help to such governmental agencies as the Food and Drug Administration by lending support to good legislation and vigorously opposing poor legislation.

It is my thought, then, that this Society has a broader purpose than just the annual presentation of scientific papers on therapeutics. I am very happy to report that yesterday Dr. Thomas Coogan, Chairman of the Council, has appointed a planning committee to work out and report on positive plans for the Society's future.

HISTORY OF THE AMERICAN THERAPEUTIC SOCIETY, 1947–1957*

LOUIS F. BISHOP, M.D.†

New York, N. Y.

This report covers the history of the American Therapeutic Society for the ten-year period closely following World War II.

It was at the conclusion of World War II at our meeting in Atlantic City, that I presented my last historical report. As many of you know, the history of our Society had been previously recorded by our Past Chairman of the Council, Dr. Lewis H. Taylor, covering the years from 1900 to 1936[1].

It is possible here in the brief time allotted to me to give you only some of the more important historical events in our Society during the last decade. It is also the privilege of an historian to select what he thinks important.

The Presidents of the American Therapeutic Society have played an important role in its development.

Let us turn our thoughts back to the year *1947*, at which time Dr. A Wilbur Duryee was our President.

The meeting of the American Therapeutic Society had as one of its features that year, a Round-Table Discussion on "The Management of Hypertension," discussed in its "Medical Aspects" by Dr. Irving Page of the Cleveland Clinic, in its "Surgical Aspects" by Dr. Jere W. Lord of the New York Post-Graduate Hospital, and in its "Pathological Aspects" by Dr. Roger M. Choisser of Washington. This was the beginning of a new therapeutic approach in the management of hypertension. It was interesting to see that our program included three of the outstanding leaders in this field.

Our Speaker of the Evening at the annual banquet was the Hon. J. Parnell Thomas, who subsequently made the headlines.

In *1948* we met in Chicago under the leadership of Dr. Thomas J. Coogan.

We were particularly honored at this meeting to have Dr. Austin Smith, Editor of the Journal of the American Medical Association present an outstanding paper on the subject of "Planned Research." Dr. Smith has continued to make American Therapeutic history and has been Chairman of the fine program which we have enjoyed at this meeting.

We were also pleased to have two of Chicago's outstanding physicians, Dr. Walter L. Palmer and Dr. Lester R. Dragstedt, bring to us the "Medical . . ." and "Surgical Management of Peptic Ulcer." It was at this meeting that plans were made for our Golden Jubilee.

In *1949* (our Golden Jubilee year) we met in Atlantic City, under our Presi-

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† Historian of the Society. Address: 141 East 55th Street, New York, N. Y.

[1] The history of the Society for 1936–1946 was written by the author, and published in Volumes 48 and 49 of the Transactions of the American Therapeutic Society.

dent, Dr. Hal M. Davison[2]. At that meeting Dr. Davison's Presidential Address was entitled "A Doctor's Philosophy," and it will long be remembered as a contribution to our Society. Dr. Davison was one of our most beloved members and his death has been a great loss to us.

At our meeting that year we heard—some of us for the first time—Dr. Alfred Blalock of Johns Hopkins present the "Surgical Treatment of Congenital Heart Disease."

Also on this program was an important Symposium on "Factors in Blood Coagulation and Clinical Use of Anticoagulants." Taking part in this Symposium were Dr. L. M. Tocantins of Philadelphia, Dr. Frank W. Konzelmann of Atlantic City, Dr. A. Wilbur Duryee of New York, Dr. E. Stirling Nichol of Miami, Dr. Joseph F. Borg of St. Paul and Dr. Gerald H. Pratt of New York.

It was fitting that our Speaker of the Evening at the Fiftieth Anniversary banquet was Dr. Reginald Fitz of Boston, one of our old and distinguished members, who spoke on "The Whole Secret of Keeping Fifty Years Young."

"Greeting and Salutations from the West" came from "Father" Pottenger, past president as well as oldest member.

In *1950* we moved on to Boston. Our President was Dr. Daniel L. Sexton of St. Louis. We met just before the American College of Physicians. It has been the custom of our Society to meet from time to time before the American College of Physicians as well as before the American Medical Association. Again that year an outstanding therapeutic advance was presented to our Society in the form of a Symposium on "ACTH and Cortisone." Taking part in this Symposium were Dr. Willard O. Thompson of Chicago, Dr. George Thorn of Boston, Dr. W. Paul Holbrook and Dr. Donald F. Hill of Tucson (joint presentation), and Dr. Francis M. Pottenger, Jr. of Monrovia, California.

The Speaker of the Evening at the annual banquet was Dr. Leland S. McKittrick, whose talk was entitled, "The Doctor Has a Patient."

In *1951* we again met in Atlantic City under the guidance of the late Dr. James Alexander Lyon. If I may depart from the strictly historical aspects of this review, I wonder how many of you knew of Dr. Lyon's military career. Dr. Lyon, besides a long and distinguished career as a physician was an outstanding soldier. He entered the military service in 1916, participating in the battles of Champagne-Marne, Aisne-Marne, St. Mihiel, Ile de France, Lorraine, Defense of Toul and Meuse-Argonne. For this he received citations from both the United States Army and the French Army Corps, and was decorated with the Silver Star, Purple Heart, Military Order of Carabao, and Croix de Guerre with Gold Star from France.

There were many fine contributions on the program that year, including a report by our former President and Chairman of the Council, Dr. Alphonse McMahon, on the difficult subject of "Hypercholesterolemia."

It was in 1951 that Dr. Oscar Hunter died. As Dr. Hunter and his family had been the "backbone" of the American Therapeutic Society, it suffered its greatest loss. I think I can express the feeling of our members that after the death of

[2] Dr. Davison died April 26, 1958.

Dr. Hunter, we felt a great obligation to carry on this Society, not only in its tradition, but to develop it to greater heights during the coming years.

In *1952* the 53rd Annual Meeting took place in Chicago with Dr. Wendell B. Gordon as our Presiding Officer. One of the highpoints of this meeting was the First Annual Lewis H. Taylor Lecture given by Dr. Karver L. Puestow, Clinical Professor of Medicine at the University of Wisconsin Medical School, on the subject, "Changing Concepts of Intestinal Function." The establishment of an important lectureship such as this enabled our Society to invite yearly an outstanding investigator in the field of therapeutics. This has contributed to the development of the American Therapeutic Society and is now an established yearly event.

In *1953* we met in New York under the presidency of Dr. Francis M. Pottenger, Jr.

It was at this meeting that Dr. Pottenger and the American Therapeutic Society representatives met with the President (Willard O. Thompson) and representatives of the American Geriatrics Society and arranged for publication of our program papers each year in the American Therapeutic Society number of the Journal of the American Geriatrics Society.

This meeting had a most interesting Symposium on Tobacco, presided over by the Professor of Therapeutics at New York University, and one of our members, Dr. Arthur C. DeGraff. Taking part in this Symposium were Dr. Harvey B. Haag of Richmond, Dr. W. C. Spain of New York, Dr. Robert C. Batterman of New York, Dr. H. Randolph Unsworth of New Orleans, Dr. A. Wilbur Duryee of New York, Dr. Grace Roth of the Mayo Clinic, and Dr. Ernest L. Wynder of Memorial Hospital, New York. It is fair to say that this was one of the most outstanding discussions on this subject ever presented before a medical audience.

In 1953 for the first time, abstracts of our papers were required in advance; and for the first time since the founding of the Society, the format of our program was necessarily larger, although still printed in white and green—the traditional colors of the American Therapeutic Society.

The Second Annual Lewis H. Taylor Lecture was presented by Dr. Charles P. Bailey, Director of The Charles P. Bailey Thoracic Clinic, Philadelphia, on "Recent Advances in Cardiac Surgery."

Our Speaker of the Evening at the New York meeting was Dr. Francis M. Pottinger; his subject was "Sixty Years in Medicine."

Many of you will remember that at this banquet the story about the clerk at the Hotel Biltmore was told for the first time by Dr. Alphone McMahon in its proper setting—namely, the Hotel Biltmore, where the meeting was held.

In *1954* the meeting of the American Therapeutic Society preceded the meeting of the Southern Medical Association in St. Louis.

This was fitting, as Dr. Alphonse McMahon had been honored by his election as President of the Southern Medical Association. It was also fitting that our President in 1954 should have also been born in the South—Dr. William B. Rawls.

One of the highlights of this meeting was a Symposium on "Electrolyte Disturbances," presided over by Dr. E. Sterling Nichol of Miami. Taking part were Dr. George T. Harrel of Gainesville, Florida, Dr. Frank W. Konzelmann of Washington, and Dr. Donald W. Selding of Dallas.

The Third Annual Lewis H. Taylor Lecture was presented by Dr. Edward H. Reinhard, Associate Professor of Medicine and Radiology, Washington University School of Medicine, St. Louis, on the subject of "Therapy of the Leukemias and Lymphomas."

Dr. Rawls, besides acting as President, presided as Toastmaster at our banquet, where a most interesting speaker, Mr. Bob Burns, Sports Editor of the St. Louis *Globe-Democrat* spoke on "The Dangerous Side of Sports."

The *1955* meeting of the American Therapeutic Society took place in Atlantic City. This meeting was held under the leadership of Dr. Harvey B. Haag, and was perhaps one of its most important, historically.

The Committee on Scientific Awards with Dr. Harry E. Ungerleider as Chairman had met to decide on the First Oscar B. Hunter Memorial Award in Therapeutics. It had chosen as its first recipient, Dr. Jonas E. Salk for his discovery of the vaccine for the prevention of poliomyelitis. In what was a truly historical occasion, Dr. Salk presented almost for the first time before a medical audience, the research that led to the perfection of the Salk vaccine. It is noteworthy that our Society was among the first to recognize him by an award.

The Fourth Annual Lewis H. Taylor Lecture was presented by Dr. Philip A. Tumulty, Associate Professor of Medicine, Department of Medicine, The Johns Hopkins University, Baltimore, on the subject of "The Natural Course of Systemic Lupus."

It is fair to say that this was one of our outstanding programs. Every paper was of high scientific excellence.

Recognizing some of the social problems of the American Therapeutic Society, it was interesting that the address of our President, Dr. Haag, should have been on the subject, "Blood and Urinary Changes in Acute Experimental Alcohol Intoxication."

In *1956* our Annual Meeting was held in Chicago. Dr. Fred E. Ball had been chosen President.

The Second Oscar B. Hunter Memorial Award in Therapeutics was presented to Dr. E. M. Geiling, Professor of Pharmacology and Chairman of the Department, University of Chicago. His address was entitled "The Value of the Radioactive Isotopes in Pharmacologic Research."

The Fifth Annual Lewis H. Taylor Lecture was delivered by Dr. Richard B. Capps, Associate Professor of Medicine, Northwestern University Medical School, Chicago, on the topic, "Hepatitis: Problems in Epidemiology and Treatment."

One of the outstanding events on this program was a Panel on "Respiratory Disease" from the therapeutic standpoint. Taking part were Dr. Albert H. Andrews, Jr., Dr. Paul H. Holinger, Dr. Karl H. Pfeutze, Dr. Harry F. Dowling,

and Dr. Robert J. Jensik, all of Chicago. Dr. G. E. Wakerlin, Chicago, acted as moderator.

Our *1957* meeting was again held in New York, under the leadership of Dr. Gerald Pratt.

The scientific program of the meeting in New York was of unusual interest, as we had 3 symposiums: one on "The Newer Aspects of Therapy in Hematology" with Dr. Paul Reznikoff of New York as moderator, one on "The Newer Aspects of Antibiotics" with Dr. William B. Rawls of New York as moderator, and one on "The Management of Hypertension" with Dr. George A. Perera of New York as acting moderator.

The Third Oscar B. Hunter Memorial Award in Therapeutics was given to Dr. Robert Wallace Wilkins, President-elect, American Heart Association, and Professor of Medicine, Boston University School of Medicine, Boston. Dr. Wilkins spoke on the treatment of hypertension under the interesting title, "From Snake Root to Serotonin."

The Sixth Annual Lewis H. Taylor Lecture, presented by Dr. Irving S. Cooper, Director, Department of Neurological Surgery, St. Barnabas Hospital, New York, was entitled "The Therapy of Parkinson's Disease."

For the first time in a number of years we did not have an after-dinner speaker at the banquet, but an excellent dinner-dance was thoroughly enjoyed by our members.

SUMMARY

Briefly, this is an outline of some of the highlights of our meetings. During the past ten years, the American Therapeutic Society has made many notable advances in its organization. The establishment of an important Lectureship; the founding of an award in Therapeutics in memory of one who did so much for our Society; a new method of publication of our papers; the constant striving for improvement of our scientific programs and the increasing number of young, active members have contributed to its development.

I cannot at this time name all the chairmen of the important committees, nor all the changes that have taken place in the Council. Their devotion to this Society is well known to our membership.

The fact that Dr. Oscar B. Hunter could succeed his father as Secretary, and carries on his work, has added greatly to the development of our organization.

Finally, history and time have not changed the "character" of the American Therapeutic Society. I should like to close with a remark my father made many years ago to Dr. Taylor:

"I hope the American Therapeutic Society will never cease its habit of informal familiar discussion of its problems. It is like a large family, meeting on common ground, friendly and helpful, tolerant of others' opinions and always courteous, one to the other. It is this, Doctor, that makes me like it, and it is this that makes me return year after year to its meetings."

THE DEFINITION AND DIAGNOSIS OF HYPOTHYROIDISM*

(The Lewis Harvie Taylor Memorial Lecture)

PAUL STARR, M.D.

University of Southern California School of Medicine, Los Angeles 33, California

INTRODUCTION

Epochs in the development of medical knowledge of hypothyroidism in modern times may be briefly delimited as: the period from 1873 to 1892, during which there was clinical recognition of Gull's disease; from 1892 to 1927, the initial period of the use of desiccated thyroid and thyroglobulin in the therapy of myxedema; from 1927, when Harington synthesized thyroxine, until 1951, during which time the measurement of the serum protein-bound iodine came into clinical use; and from 1951 on, the year in which Pitt-Rivers, carrying on in Harington's laboratory, investigated triiodothyronine and began the synthesis of the thyroxine analogues.

DEFINITION

Hypothyroidism is a condition of the body in which there is insufficient thyroid hormone in the tissues to maintain certain chemical reactions at their normal rates. The condition of the thyroid gland controls this end-result but studies directed to the thyroid gland do not necessarily reveal the amount of free thyroxine in the tissues. By definition, we are interested in the condition of the body as effected by thyroxine and not in the condition of either the thyroid or the pituitary gland.

A brief statement, however, of the mechanisms controlling the supply of thyroxine to the tissues is pertinent.

MECHANISM OF HOMEOSTASIS

The thyroid gland is part of the homeostatic mechanism that maintains the requisite concentration of thyroxine in the cells of the body. This mechanism, which probably does not have "feedback" characteristics, involves 1) the peripheral tissues, 2) a means of communicating their need for thyroid hormone to a responsive center in the brain now identified as the paraventricular nuclei, 3) the portal vessels which convey a TSH-releasing factor from these nuclei to the adenohypophysis, 4) the thyrotropic hormone elaborated by the pituitary, 5) the general circulation which carries this hormone to the thyroid, 6) the responsive parenchymal thyroid tissue, and 7) the general circulation which carries the thyroid hormone to the tissues, where it serves its vital function in cellular metabolism. The rate of thyroidal secretion is controlled by the need for hormone in the body tissues as a whole, rather than by the concentration of hormone

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circulating through the adenohypophysis. Thus when animals are warmed, the thyroid becomes less active; when they are chilled, it is stimulated to greater activity.

ETIOLOGIC CLASSIFICATION

Hypothyroidism may be classified by the element in this homeostatic mechanism which is disordered. Thus there is hypothalamic hypothyroidism resulting from damage to the hypothalamus. Clinical myxedema has been reported after encephalitis and it may be assumed that many persons suffer from dysfunction of this major portion of the autonomic brain.

Hypopituitary hypothyroidism may be complete in Sheehan's syndrome following pituitary infarction associated with shock due to childbirth. There are, however, many mild hypopituitary insufficiencies, sometimes general and sometimes mono-hormonal, which lead to reduced TSH secretion and partial hypothyroidism.

Thyroidal hypothyroidism is probably not more common than the thyroidal deficiencies resulting from the malfunction of the hypothalamus or pituitary. The failure of the gland to produce normal amounts of thyroxine may be due to an intrinsic biochemical defect, or to destruction of the epithelium by disease or treatment.

A fourth variety of hypothyroidism may be postulated at the beginning of the chain, namely, in the tissues. It is conceivable that, in the presence of a normal amount of free thyroxine, the enzyme systems usually catalyzed would be deficient or unresponsive. Thus, there may be a somatic form of hypothyroidism.

The chemistry of the thyroid hormone has undergone the same type of evolution that has occurred in the chemistry of adrenal steroids. Cortisone, hydrocortisone, prednisone, prednisolone, methylprednisone, and now, triamcinolone, were produced in rapid succession. These were developed because they were found to have slightly different metabolic actions. Thyroxine was synthesized by Harington in 1927, but little advance occurred after this for nearly twenty-five years. In 1951, as a result of chromatography and radioactive iodine, a new era in thyroid biochemistry began. Triiodothyronine, diiodothyronine, tetraiodo- and triiodopropionic, pyruvic, lactic, butyric and acetic-acid analogues were formed. Tetraiodothyroformic acid had been synthesized by Harington as early as 1927 but it was not until 1957, thirty years later, that it was shown to have no antigoitrogenic activity, as compared to levo-thyroxine, but twice as much cholesterolytic effect. Fundamental postulates of the molecular function of thyroxine were formulated by Niemann (1941), Lipmann (1951), and Bruice, Kharasch and Winzler (1954).

Much interest has been created by a recent clinical interpretation of the theory that thyroxine must be deiodinated into triiodothyronine before it can act as thyroid hormone. (Incidentally, we have failed to demonstrate this after three years' experimentation.) A group of patients complaining of all the ills that flesh is heir to, were said to be unresponsive to desiccated thyroid or sodium levothyroxine, presumably because they lacked the necessary biochemical function. They were said to be in a state of hypometabolism or metabolic insufficiency.

Heat production was somewhat reduced but, in our view, thyroxine metabolism was normal. The serum protein-bound iodine level was normal, the thyroidal radioactive iodine uptake was normal, but still these patients had complaints. Whereupon, they were given triiodothyronine without any biochemical or metabolic demonstration that there was thyroid insufficiency. The symptoms disappeared. No placebo was given, and there was no double-blind therapeutic trial. The effects of tranquilizers and agitators were not determined. The relief of symptoms was taken to prove the presence of a metabolic disease specifically due to insufficiency of triiodothyronine. One might as well say that defervescence following salicylate therapy proves that pneumonia is a state of willow-bark depletion. No matter how absurd this sounds, it might be true! Unfortunately, it is not clear that enough thyroxine had been administered to create a high concentration of protein-bound iodine or that the effect of triiodothyronine was biochemical rather than psychologic, and moreover, that it was healthy. Triiodothyronine is a potent stimulant, particularly for the sympathetic nervous system, and it may well be that the complaining patients received a jolt which satisfied their demand regarding symptoms but which did nothing to improve their health. Keating, in an editorial in the May 1958 issue of the Journal of Clinical Endocrinology and Metabolism, concludes "physicians will be well advised to decide between well-reasoned experimental hypotheses and clinical observation on the one hand, and overenthusiastic and irresponsible advertising on the other."

The diagnosis of hypothyroidism at present depends mainly on indirect evidence: 1) the amount of thyroxine in the serum, measured by means of the concentration of protein-bound iodine, and 2) the condition of the thyroid gland indicated by the radioactive iodine uptake. In the future a third measure, namely, the bioassay or chemical measurement of pituitary thyrotropic hormone will be important; it is impossible now.

The right honorable *basal metabolism test* is a direct determination of the action of the thyroid hormone in the tissues, producing heat and increasing oxygen utilization. In this sense, it should be a reliable method for determination of the hypothyroid state. However, in clinical practice, this test has been deceptive. So many other mechanisms influence oxidative energy that it is possible for a completely athyreotic patient to register a normal basal metabolic rate. The major component of these nonthyroid oxygen-using systems is skeletal muscle. Many years ago, Roy Hoskins astounded his associates by claiming that he could alter his metabolic rate by an effort of the will. He did. Following in his footsteps, I had a basal metabolism test one day, with the result that it was −6 per cent. Then, without informing the technician of my experiment, I asked her to repeat it. During this second test, I pretended that the lighting fixture in the ceiling was going to drop on me and I kept myself in a state of racing readiness to jump out from under. I made no movement, made no *voluntary* muscle contraction, but my pulse was more rapid, my respiration quicker, and the metabolic rate +15 per cent—a rise of 21 points. The time interval between these 2 tests was one minute. Such a rise might be due to induced increased muscle tone.

Hence a hypothyroid patient whose true basal metabolic rate is probably −20

per cent, may easily register several consecutive normal rates. As we have observed, even an athyreotic patient can register a normal basal metabolism. In these cases the physician receives misinformation. The technician performing the test has no way of knowing whether the patient is in a basal condition, or (as I was) tense because of impending danger.

But more difficult to analyze is the nonspecificity of the test. Suppose that, because of superior good will and cooperativeness, a patient registered a truly basal metabolic rate, and that it proved to be subnormal. This comparatively reduced oxygen consumption might be due to reduced muscle mass and tone, excessive fat or edematous tissue, lowered secretion of the adrenal cortex or gonad, or even pathologic depression of the seat of the soul, the hypothalamus. Nothing in the result, expressed as calories per square meter per hour, indicates which of these conditions is present. It is quite possible to have marked hypometabolism with normal thyroid function. (In passing, it would not seem sensible to alter this state by administering thyroid hormone.)

Another thing wrong with the basal metabolic rate test is the usual technique. In a strange room in a hospital or laboratory, after being awake without breakfast, without cigarette, without coffee, the patient is told to lie there for another half hour. The technician leaves, and presently the patient begins to wonder whether he has been forgotten. In another few minutes this becomes a certainty. He is prepared to get up and go find the technician. Then, he realizes with chagrin that the test is going to cost him ten dollars. Just then, the technician comes back and fills a machine with gas, thrusts a large rubber gag into the patient's mouth, tells him to breathe through it, and pinches his nose so tightly with a clamp that it begins to get hot and thumps with the angry beat of his heart. When the choking respirations are finally going through the rubber pipe into the machine, the patient begins to realize that he has to push the air out and pull it in. This goes on interminably, but actually for only six minutes. The registered change in oxygen volume which has occurred in this brief uncomfortable experience is then multiplied by 10 to represent an hour of your life. All the erroneous characteristics of the test are thus exaggerated tenfold. The result is your basal metabolism! It is a wonder we get any useful data at all, even if we don't know what it means!

Recently, we acquired a Noyans Diaferometer. This is an open-circuit instrument developed in Holland, which analyzes the expired air mixed with a known flow of room air. The oxygen content and carbon-dioxide content are determined by electrical changes recorded by galvanometry. The rates of oxygen removal and carbon-dioxide addition are determined, the rate in terms of calories per square meter per hour can be calculated constantly from moment to moment, and the respiratory quotient is obtained simultaneously. Best of all, the patient's head and neck lie comfortably in a little plastic tent with no obstruction to breathing, no gag, nose clip or mask, and no time limit. We are expecting great things of this instrument. This may give us true basal metabolic rates; furthermore, the prolonged time period will permit acute experiments—pharmacologic tests, which may demonstrate the nature of the metabolic rate.

For the present, since the basal metabolic rate test is not always reliable, we can turn to measuring the amount of thyroid hormone in the circulating blood by determining the *serum concentration of protein-bound iodine* (*PBI*). This measurement is made by chemical methods that are remarkably accurate for the amount of substance being determined. The laboratory error is less than 1 microgram (μg.) in the low hypothyroid range, about 1 μg. in the euthyroid range, and 2–3 μg. in the hyperthyroid range.

According to several authors, the normal range for serum PBI is 4 to 8 μg. per 100 ml. The criteria of healthiness for the subjects from whom blood was obtained for this normal range of values is nowhere stated precisely. The usual way of obtaining a range of normal values for any laboratory procedure is to test the people around you in the college or medical school in which you happen to be working. If the subject is ambulatory, attending classes, and can pass a life insurance physical examination, he is in—particularly if one of the senior clinicians inspects him and says, "he's normal." I must not be too sarcastic, as I haven't anything much better to offer as yet. It seems likely that as means of measuring the spectrum of the physiologic and biochemical effects of thyroxine become available we shall be able to establish normal values more precisely. Barker originally stated that the range was 3.5 to 8.5 μg. per 100 ml., as determined in 100 U.C.L.A. associates selected by the method just described. VanderLaan recently reported a normal range of 4 to 8 μg. per 100 ml. Probably there are 2 normal ranges—one for adult males (5 to 7 μg.), and one for adult females (6 to 8 μg.)—but I can't prove it.

In this laboratory, for the normal range of protein-bound iodine concentration we use 4 to 8 μg. per 100 ml. of serum. We classify patients who have serum PBI levels between 4 and 5 μg. per 100 ml. as functionally hypothyroid; those with levels between 3 and 4 μg. as moderately hypothyroid; those with levels between 2 and 3 μg. as severely hypothyroid, and those with levels below 2 μg. as totally athyreotic. We are not sure what the PBI is composed of in this lowest range; it may not be thyroxine.

The concentration of inorganic iodide in the serum should always be estimated approximately and reported to the physician. This is often not done. According to VanderLaan, if the inorganic iodide level is above 2 μg. per 100 ml., the patient must be ingesting unusual amounts of iodide; at just what level the iodide combines with protein to raise the PBI value with added nonthyroxine iodine is not determined. Inorganic iodide values over 10 μg. per 100 ml. should invalidate the PBI report, and call for an attempt to identify the source of iodide and repeat the test when it has been reduced.

Many organic iodine medications and roentgenographic dyes become bound to protein, give rise to nonthyroxine PBI values, and recirculate in the body for months and years. If the amount of iodide is high enough, these substances lower the thyroidal uptake of radioactive iodine and thus disclose their true nature.

The thyroxine secreted *in vivo* by the gland, as well as thyroxine administered in the form of animal desiccated thyroid or thyroglobulin, or as synthetic sodium levo- or dextro-thyroxine, is bound by one of the serum proteins. This

protein is an inter-alpha globulin, often called *thyroxine-binding globulin or TBG.* The protein-bound iodine we measure in the clinical laboratory includes the iodine in this bound thyroxine as well as that in free thyroxine, *i.e.*, all the amino-acid organic iodine. To an unknown extent the amount of the thyroxine-binding globulin effects the level of the serum PBI, if the gland is able to increase the secretion of thyroxine as the binding capacity increases. This occurs in normal women during pregnancy; the TBG increases and the thyroid responds with a slight rise in the amount of transported circulating thyroxine. The serum PBI level in pregnancy may be increased as much as 50 per cent, but there is no thyrotoxicosis; if anything, there is less free thyroxine available than when the concentrations of TBG and PBI were lower. In the few cases of myxedema (nonpregnant) which we have studied in this respect, the concentration of TBG was abnormally elevated whereas that of PBI was at the myxedema level—about 1 to 2 μg. per 100 ml. It seems possible that in partial hypothyroidism, if the serum PBI level were elevated, the thyroid would not be able to raise the output of combined thyroxine sufficiently and thus the hypothyroidism would be aggravated by prevention of the formation of free thyroxine. Vice versa, if the serum TBG level were unusually low, a low PBI level and an inadequate thyroid gland might be associated with an unusually high amount of free thyroxine; thus there might be no hypothyroidism at all.

However we do not know whether or not affinity or release of thyroxine from the binding globulin would be different in various clinical states; and, furthermore, were TBG adjusted to allow more free thyroxine, whether or not this adjustment would be sufficient. It is clear that there is no linear relationship between the amount of TBG and the concentration of PBI, and also clear that TBG is not obligatory for transport. We have made observations on a man who appeared to be euthyroid. His serum PBI level was only 2.8 μg. per 100 ml. and there was no thyroxine-binding globulin by electrophoresis; the thyroid hormone was being distributed by the circulation without protein binding. This also occurs with triiodothyronine. For instance, in a myxedema patient with a serum PBI level of only 1.0 μg. per 100 ml. and a BMR of −40 per cent, daily administration of enough triiodothyronine to increase the basal metabolism to normal did not produce any detectable increase in the serum PBI level in the 10-ml. sample used for the determination. The triiodothyronine was reaching the tissues through the circulation without accumulating in the blood.

Using the serum PBI value as an imperfect but still the best means for diagnosis of thyroid deficiency, we made a survey[1] of the *incidence of hypothyroidism among men in industry* in Southern California. Thirteen cooperating companies and their medical directors sent us blood samples, by mail, from male employees. These employees were not sick; they were seen because of re-employment examination or for a similar administrative reason. Seven per cent of them had serum PBI levels of less than 4 μg. per 100 ml. By this definition they were hypothyroid. Suppose that a third of them (those with PBI values nearest 4 μg.) were actually not hypothyroid, that the TBG value was low and the free thyroxine value

[1] Supported by the Warner-Chilcott Laboratories, Morris Plains, New Jersey.

normal, or that thyroxine action was unusually potent because of susceptible substrates, this would still leave about 5 per cent of the employees who might be hypothyroid. Is this absurd? On the contrary, it seems quite possible. Since census reports indicate about 19 million men in industry, 5 per cent would be about 1 million men. By comparison, public health estimates of diabetes in this country indicate that there are 3 million diabetics, half of whom do not know they have the disease. We determined the serum PBI level in about 4500 men. In a small sample of the men with low PBI values, clinical examination, including history, physical findings, blood count, urinalysis, thyroidal I^{131} uptake, and basal metabolic rate, produced definite corroborative evidence of hypothyroidism in three quarters of them. Such patients would not go to a physician, or if they did so, would not be able to give any history or show any physical finding that would lead to a diagnosis of hypothyroidism. Hence, the serum protein-bound iodine test should be carried out in all patients as a screening procedure, in the same way that the urine is tested for sugar to detect diabetes.

Classification. It is all very well to define hypothyroidism as the condition created by an insufficient supply of the thyroxine necessary to maintain substrate chemical reactions at their normal rates, but we do not know what these reactions are. In lieu of facts in this field, a suggestive scheme has occurred to me. There are 4, if not more, thyroid hormones—thyroxine, triiodothyronine, triiodothyroacetic acid (triac), and tetraiodopropionic acid (tetraprop). Although we know of few specific chemical processes influenced by these molecules, perhaps their functions can be classified as follows:

I. Oxidation, or heat production.
II. Adrenergic synergism, perhaps permissive in relation to epinephrine effect.
III. Cholesterolysis (either excretion or utilization of cholesterol).
IV. Growth, or metamorphosis.

Much more sensible divisions of thyroid hormone functions will be made when the catalytic action of these 4 molecules is known. But one could suppose, in planning research, that thyroxine might be important for group I (oxidation), triiodothyronine for group II (adrenergy), triac for group III (cholesterolysis), and tetraprop for group IV (growth or metamorphosis).

In the light of this theory, if we were to study intelligently a case of suspected hypothyroidism, we should study such processes, because possibly one or more might be normal, whereas one or more might be subnormal. This requires that we consider the means for measuring these chemical processes.

If the new instrument works and physiologic identification becomes possible, we may be able to estimate how much of the BMR is thyroxine-dependent, and thus be able to use the first of our 4 parameters of hypothyroidism.

To determine the second, namely, synergism with the sympathetic nervous system, an entirely different approach is needed. Some ancient experiments going back to 1911, and recent work in the last three years from Harvard, Washington University in Seattle and State University of New York in Brooklyn have shown that epinephrine acts via thyroxine or one of its analogues. The athyrotic

animal, having no thyroid hormone, does not produce more heat when given epinephrine. More important, the response of the heart to epinephrine was found to be a function of the amount of thyronine present. This is a revival of the Goetsch test that some of us remember. It seems to me that by these definitions, a person might have normal heat production (*i.e.*, enough thyroxine) but poor epinephrine responsiveness due to an insufficiency of triiodothyronine. The studies referred to have produced significant data, but the interpretation and application remain to be elucidated.

Suggestions for detecting this form of hypothyroidism are inherent in these studies. Administration of known amounts of epinephrine at certain rates under certain conditions should, in a euthyroid person, elicit the characteristic acceleration of pulse and increased cardiac output. The results in a hypothyroid or a triiodo-hypothyroid person would be subnormal. Such tests, carried out following the basal metabolic rate determination, would clarify another facet of hypothyroidism.

The third form of hypothyroidism postulated was that associated with the chain of events which produces hypercholesterolemia. Trotter and associates demonstrated clinically that triiodothyroacetic acid (triac) reduces the serum cholesterol level without elevating the basal metabolic rate to the expected extent. Unfortunately, this cholesterolytic, or possibly antiatherogenic, effect appears to wear off even with continued, supposedly adequate dosage. Perhaps the primary effect is dependent on ratios of products which would be restored by other analogues, for instance thyroxine itself. At any rate, the biochemical control of hypercholesterolemia seems associated with triiodothyroacetic acid. The dissociation of severe hypo-oxidation, or thyroxine hypothyroidism, from hypercholesterolemia occurs in an occasional myxedematous patient having a basal metabolic rate commensurate with athyreosis, but a normal level of serum cholesterol. In our industrial survey of the incidence of hypothyroidism, low serum protein-bound iodine values were commonly found in association with normal serum cholesterol values.

Another experimental approach to the question of the independence in function of thyroxine derivatives from that of thyroxine itself is provided by our studies with dextro-thyroxine[2] (Dr. Leonard Ginger). Dr. Ginger made sodium dextro-thyroxine free of the levo isomer. When a dose of from 4 to 12 milligrams of this material is given daily by mouth to patients having hypercholesterolemia, there is almost no effect on the basal metabolic rate or on the heart, but there is a significant fall in serum cholesterol concentration. This would appear to be due, not to the dextro-thyroxine itself, but possibly to a deaminated thyroxine derived from it. The derivative acts without the presence of levo-thyroxine or triiodothyronine, since there is no increase in heat production or in sympathetic nervous action on the heart.

The fourth category of biochemical phenomena influenced by thyroxine or its analogues concerns growth and development. It has been clearly demonstrated

[2] Project support and supplies of mono-isomeric sodium dextro-thyroxine were received from Baxter Laboratories, Morton Grove, Illinois.

by controlled animal experimentation that thyroxine or a derivative synergizes with growth hormone. In clinical experience, delay in growth to the point of dwarfism results from complete or partial hypothyroidism. This phenomenon seems to indicate a completely different biochemical process from that of the catabolism characteristic of hyperthyroidism, with its high caloric consumption. In growth, more food is used, but anabolism results.

One of the most important biologic mysteries is metamorphosis. Tadpoles become frogs. Human fetuses become babies. Babies become children. Boys and girls become men and women. Is there a connection between the processes that turn larvae into frogs and those that turn infants into adults. Who knows? This experimental field has recently been used to demonstrate the difference in action of thyroxine analogues. In 1914, Gudernatsch in Munich discovered that administration of thyroid accelerated the metamorphosis of *Rana pipiens*. This was a quantitative function of the thyroid hormone. In 1955, in the organic chemistry department of the University of Southern California, Bruice was able to compare the metamorphic effects of many thyroxine molecules. In *Rana catesbiana*, tetraiodopropionic acid, one of the 3 deaminated tetraiodothyroxines, was found to be sixty-five times as potent as its parent molecule. Tetraprop, as it is called, accelerates the process of metamorphosis far more effectively than does thyroxine itself. This suggests that the biochemical processes involved may not normally be catalyzed by thyroxine but by its deaminated products.

If this acceleration of metamorphosis and/or growth is not due merely to increased heat production, to action on the sympathetic nervous system, or to the processes associated with cholesterolemia, it must depend on an important chain of chemical reactions catalyzed not by thyroxine, triiodothyronine or triac, but especially by deaminated thyroxine. Possibly delay in metamorphosis and growth is a special form of hypothyroidism. How this may be demonstrated in the adult who is not getting bigger and who is having the reverse of metamorphosis as he gets older, remains to be seen. Certainly, our epidermis grows, our red cells multiply, and our white cells metamorphose from the mononuclear to the polymorphonuclear form. Perhaps these systems would be suitable for new studies.

To add the final touch—suppose we assume that cancer of an organ is the failure of its youngest cells to metamorphose into the normal adult form. If so, cancer is the result of this particular form of hypothyroidism!

The interpretation given here of the biochemical functions of thyroxine and its derivatives is quite different from that of the biochemists who discovered these compounds. As each compound has appeared, these scientists have concluded that the new form was *the* thyroid hormone. The greater potency per milligram was taken to indicate that all thyroid function was confined to that molecule. Thyroxine was not the thyroid hormone because the calorigenic push of triiodothyronine was quicker; then triiodothyronine was not the thyroid hormone because triac was still quicker. It seems possible that although the functions of these molecules are different and they have distinct metabolic pathways, they are all thyroid hormones.

ENHANCEMENT OF SODIUM SALICYLATE ABSORPTION AND CLINICAL EFFECTIVENESS BY MEPHENESIN*

ROBERT C. BATTERMAN, M.D., JULIUS CARR, Ph.D. AND GEORGE J. MOURATOFF, M.D.†

The Department of Medicine and Arthritis Services of New York Medical College-Metropolitan Medical Center, Flower and Fifth Avenue Hospitals, Metropolitan Hospital, and Bird S. Coler Memorial Hospital and Home, New York, N. Y.

The treatment of any arthritic condition depends upon integration of 3 basic therapeutic regimens. Foremost is the use of specific therapy of proven merit whenever such is available. Second, in almost all cases, it is necessary to use corrective and preventive measures for deformities, mechanical difficulties and postural abnormalities. The third aspect of treatment is the institution of symptomatic therapy to alleviate the painful state until "specific" or corrective measures become effective. Unfortunately, symptomatic therapy has been neglected in recent years. The advent of steroids and the introduction of potent antirheumatic drugs have raised our hopes that these are the answer for all arthritic patients. Experience with these medications (1), however, has demonstrated that their usefulness is limited and that they are not devoid of serious toxic manifestations. Their use has served nevertheless to disclose two aspects of treatment of the arthritic patient. The first is the recognition that with few exceptions the patient with "arthritis" has a chronic disease. The practicing physician should give this fact consideration when any therapy is chosen. No matter how satisfactory a drug may be when first administered, the need for continued use may alter the overall response. Tolerance and cumulative toxicity may detract from the early enthusiasm accorded many of the newer antirheumatic drugs. The occurrence of tolerance and cumulative toxicity has emphasized the need for effective symptomatic therapy.

An effective symptomatic medication should satisfy the following criteria—in essence the same as previously described (2) for analgesic drugs: 1) When administered in optimum dosage, the medication should alleviate pain and disability in the majority of patients. The effectiveness may be influenced by the type of "arthritic" condition under treatment but the physician should be assured that the likelihood of achieving a satisfactory analgesic and antirheumatic effect can be expected. 2) This effect should be achieved with the least likelihood of the occurrence of toxicity, either gastro-intestinal or systemic. 3) The resultant analgesia should occur promptly and provide satisfactory relief of pain for the period of time required by the clinical status of the patient. 4) Degree and duration of analgesia should not be influenced by tolerance. 5) The medication should be applicable for the relief of arthritic pain regardless of age, etiology of the disability, or accompanying conditions that may alter the elimina-

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† Fellow, Department of Hospitals.

tion or dissipation of the drug from the body. 6) Idiosyncrasies or unpredictable untoward reactions should be rare. 7) Acute and chronic administration of antirheumatic drugs should be devoid of effect upon electrolyte balance or other metabolic constituents required for normal physiologic function. 8) The medication should be free of the possibility of drug addiction in the sense that physical dependence should not occur with prolonged administration, and discontinuation of the drug should not lead to withdrawal symptoms.

A review of all drugs used for the treatment of arthritic conditions reveals that salicylates more than satisfy these criteria. The purpose of this report is to present pharmacologic and clinical data which suggest that the desirable therapeutic effect of salicylates can be potentiated or enhanced by mephenesin.

PHARMACOLOGIC CONSIDERATIONS

It has been recently discovered in our laboratory that mephenesin markedly increases the absorption of sodium salicylate from the gastro-intestinal tract in man. Details as to investigative procedure, methods of chemical analysis and comparative absorption data of sodium salicylate or aspirin with and without simultaneous administration of mephenesin have been reported (3). Figures 1, 2 and 3 summarize the pertinent data. Salicylate concentration was determined by a modification of Brodie, Udenfriend and Coburn's method (4). Figure 1 depicts the absorption of 0.5 Gm. of sodium salicylate administered alone by the oral route. This curve was obtained by utilizing data on 38 subjects; in addition to the control sample, from 1 to 3 blood samples were taken at random intervals as indicated over a period of six hours. The individual total plasma levels for each point, the composite curve for the mean of each point, and upper and lower limits of 95% confidence levels are illustrated. It will be noted that salicylate appeared in the blood in significant amounts in five minutes, reached a peak at two hours and was still evident at six hours. Figure 2 illustrates the

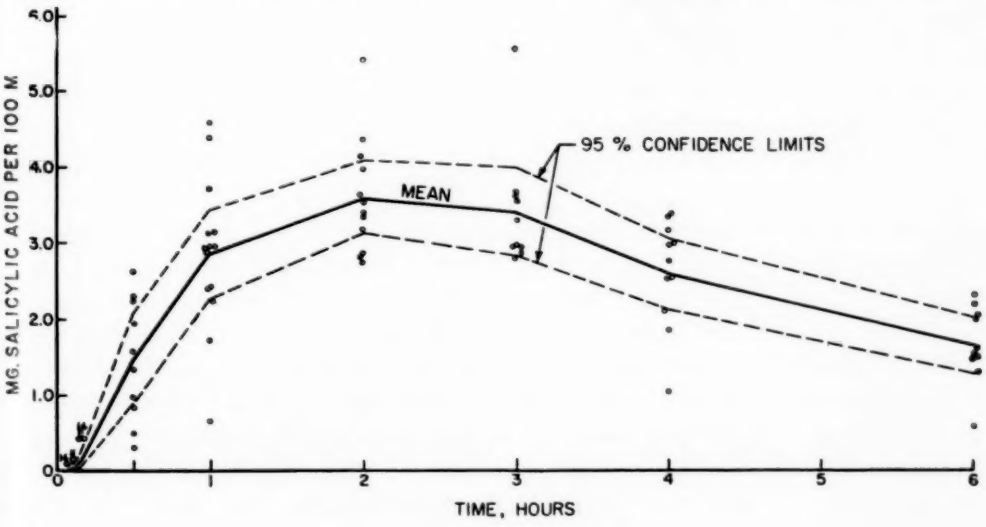

FIGURE 1

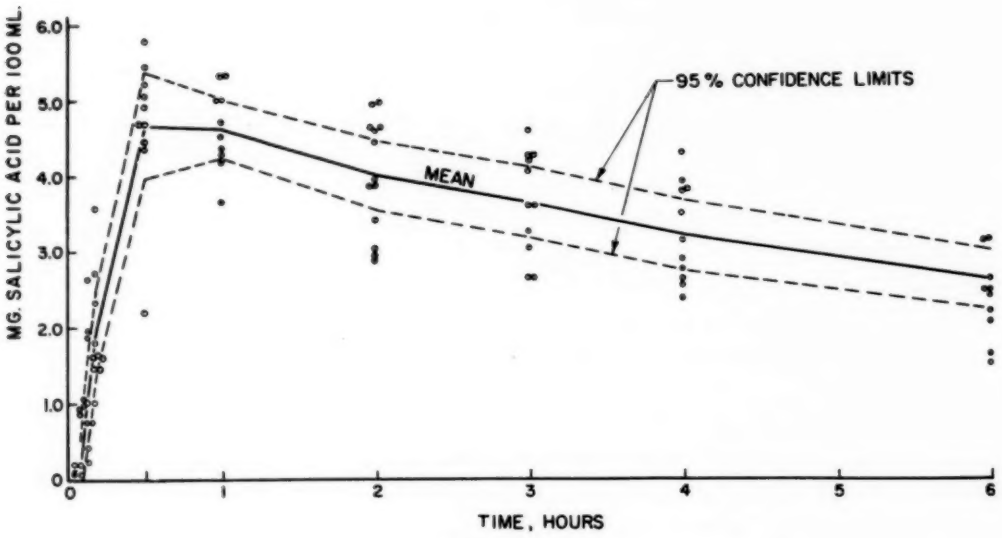

FIGURE 2

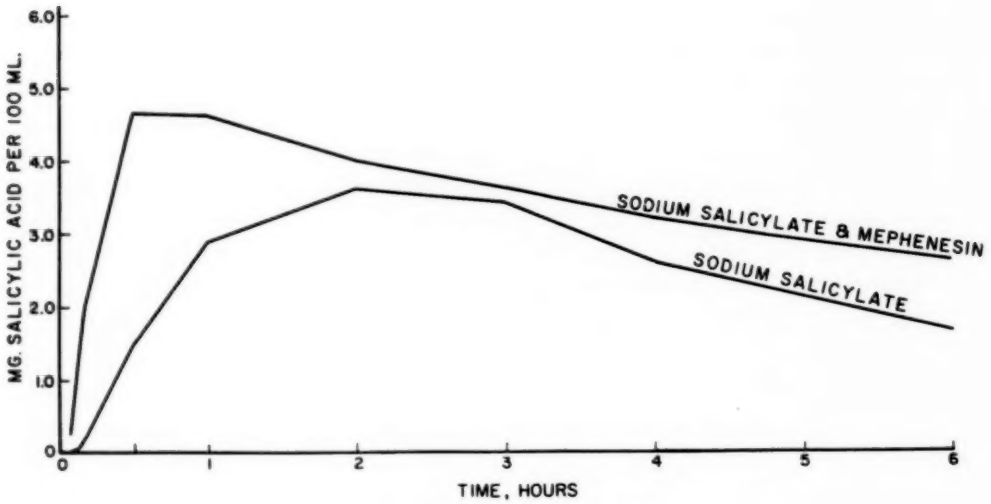

FIGURE 3

results in 46 additional subjects given a combination of 0.5 Gm. each of mephenesin and sodium salicylate. The absorption of sodium salicylate was markedly increased. At seven and a half minutes, the mean plasma salicylate level was 1.16 mg. per 100 ml. as compared with 0.06 mg. for sodium salicylate alone. The student t value of 4.59 was highly significant. At thirty minutes, at which point the peak of absorption was reached, the mean plasma salicylate level following administration of the mephenesin-sodium salicylate combination was 4.67 mg. per 100 ml. as compared with 1.46 mg. following sodium salicylate alone. The student t value of 7.99 for this 30-minute comparison was very significant. The influence of mephenesin upon the absorption of sodium salicylate is best seen

in Figure 3, where the mean curves for sodium salicylate with and without mephenesin are illustrated. Not only was the rapidity of absorption faster, as reflected in attainment of a peak effect at thirty minutes, but the total plasma salicylate level was also considerably higher than the peak achieved after treatment with sodium salicylate alone.

CLINICAL OBSERVATIONS

The next problem was to determine whether the more rapidly achieved and higher blood levels of salicylate when administered with mephenesin reflect a more effective clinical preparation. To answer this question, the combined mephenesin-sodium salicylate preparation available (Mephosal[1]) was studied as an analgesic and antirheumatic medication in comparison with placebo therapy and 2 effective drugs, sodium salicylate and aspirin. These standard medications have been repeatedly under investigation in our laboratory. Sodium salicylate alone was studied in 4 groups of patients at three dosage levels, namely, 300, 500 and 600 mg. Also included were 2 studies with aspirin (using a dose of 600 mg.), and 2 groups of patients who received placebos. In each case the medication was administered three to four times daily continuously for periods of one to several weeks. Unless an untoward reaction occurred or the medication was ineffectual, the drug was continued in all but a few instances for three weeks or longer. The patients were all ambulatory and complained of pain and/or disability of varying intensity secondary to a wide variety of musculo-skeletal conditions. With few exceptions, the patients prior to the institution of this study, had been under observation for many weeks or months. It was thus possible to have a control evaluation of responsiveness and tolerance to all of the standard medications and other analgesic or antirheumatic remedies in current medical or investigational use.

Our criteria for evaluation of such medications have been reported (5) on numerous occasions. We employ an "all or none" response. The medication must be so satisfactory in controlling the patients' pain and disability that there is never any doubt that relief has been achieved. Relief must be sustained throughout the period of drug administration and must be obtained in the majority of drug trials. The variability of the patients' response from day to day, or even from one drug trial to the next requires that only the overall effect (usually that achieved within a period of two to three weeks or longer) be considered. A decreasing response during this period, even though the drug was completely effective initially, or the occurrence of disturbing untoward reactions, classify a drug as unsatisfactory.

Results of representative past studies as well as of concurrent studies with Mephosal are summarized in Table 1. Utilizing the foregoing rigid "all or none" criteria, placebo therapy was effective in approximately 40 per cent of the patients. These results are in accord with those of all similar studies recently summarized by Beecher (6). The standard drugs—sodium salicylate alone, or

[1] The medication and other aid was supplied by Crookes-Barnes Laboratories, Inc., Mountain View, N. J.

TABLE 1

Comparative Analgesic and Antirheumatic Effectiveness

Medication	No. of Patients	Effective		Untoward Reactions	
		No. of Patients	Per cent	No. of Patients	Per cent
Mephosal (sod. salicylate, 500 mg.; mephenesin, 500 mg.)	59	41	69.5	7	11.9
Sodium salicylate, 300 mg.	41	22	53.6	7	17.1
	44	23	52.3	9	20.4
Sodium salicylate, 500 mg.	52	28	53.8	15	28.8
Sodium salicylate, 600 mg.	40	20	50.0	16	40.0
Aspirin, 600 mg.	87	45	51.7	24	27.5
	128	68	53.1	30	23.4
Placebo	49	17	34.6	6	12.0
	41	19	46.3	5	12.2

aspirin—had an analgesic and antirheumatic effect in 50 to 54 per cent of the patients. This incidence of effectiveness has never been exceeded on our arthritis service, although we have repeatedly restudied these medications. With chronic administration (at least three weeks of continuous therapy), 300 mg. was as effective as 600 mg. and the occurrence of untoward reactions was less. The influence of mephenesin upon the effectiveness of sodium salicylate was marked. Satisfactory relief of rheumatic pains occurred in 69.5 per cent of the patients. The incidence of untoward reactions with Mephosal was within the range associated with placebo level. In terms of therapeutic index, the combined mephenesin-sodium salicylate preparation reflected a decided superiority for clinical usefulness.

DISCUSSION

Pharmacologic and clinical studies indicate that mephenesin markedly influences the absorption as well as the analgesic and antirheumatic effects of sodium salicylate. Reasons for this synergism are lacking at this time. In the test tube, mephenesin and sodium salicylate enhance each other's solubility. Clinically, although the absorption of sodium salicylate is enhanced, that of mephenesin is not. Absorption of aspirin is uninfluenced by mephenesin (3). There are many questions which remain unanswered. The higher salicylate blood level with the mephenesin-sodium salicylate combination does not explain completely the greater clinical effectiveness of this preparation; similar levels may be obtained with aspirin or with large doses of sodium salicylate. However, these blood levels are slow in reaching a peak and the antirheumatic effects of aspirin and sodium salicylate alone, regardless of dose, are inferior to those of the mephenesin-sodium salicylate mixture. Perhaps the increased rapidity of salicylate absorption which occurs with concomitant administration of mephenesin plays a major role in the clinical effectiveness. This is in accord with the pharmacologic principle that the more rapidly an effective concentration of a drug is reached at the target organ, the greater the response.

The lower incidence of gastro-intestinal intolerance to the mephenesin-sodium

salicylate combination suggests that the rapid absorption of salicylate decreases or precludes the gastro-intestinal irritation which commonly occurs in arthritis patients during prolonged administration of salicylates. If so, then the intolerance which develops with prolonged use of salicylate is related primarily to inadequate absorption and sustained high concentration within the gastro-intestinal tract rather than to the salicylate chemical per se.

The influence of mephenesin upon sodium salicylate pharmacology and clinical effectiveness has initiated, at least in our laboratory, numerous studies to discover the mechanism of action. Further speculation at this time is unwarranted and contributes little in way of explanation.

CONCLUSIONS

Mephenesin greatly enhances the absorption of sodium salicylate from the gastro-intestinal tract of man and potentiates its analgesic and antirheumatic effects.

In 9 groups of patients, comparative studies with placebo therapy, sodium salicylate (3 dose levels), aspirin, and a combination of mephenesin and sodium salicylate demonstrated the superior analgesic and antirheumatic effect of the combination.

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A CRITIQUE OF THE CONCEPT OF SYMPATHETIC-PARASYMPATHETIC ANTAGONISM*†

FREDERICK H. MEYERS, M.D.‡

The Department of Pharmacology and Experimental Therapeutics, University of California Medical Center, San Francisco, California

The concept that the sympathetic and parasympathetic components of the autonomic nervous system act antagonistically to control the activity of the automatic tissues has established applicability in a very few situations—one being the control of the heart rate, for example. The idea that this balance between sympathetic and parasympathetic influences is of wide importance is derived in part from the anatomic fact of the dual innervation of some organs and in part by reasoning from the effects of injecting substances known to be chemical mediators.

There are, however, objections to any formulation which depends upon dual, antagonistic extrinsic nervous influences to explain the regulation of most of the intrinsically rhythmic tissues. These objections are most clearly defined by considering the results of chronic nerve section experiments.

Interrupting the parasympathetic ("motor") supply should, according to the usual concept, lead to a decrease in the activity of the smooth-muscle organ supplied; but such is not the case. The fundus of the stomach is indeed inhibited by vagal section, but other organs are either uninfluenced by parasympathetic denervation or react to section of the "motor" nerves by an augmentation of activity, in some cases with eventual hypertrophy.

Nor can the increased activity which usually follows sympathetic denervation be explained as being due to the unopposed action of the parasympathetic, since added parasympathetic nerve section either intensifies or leaves unaltered the hyperactive state.

This discussion suggests that a more consistent interpretation of nerve-section experiments can be derived if the mixed composition of the nerve involved is considered, namely, that interruption of sensory fibers from the organ may be more important than section of the efferent fibers. This is not a radical suggestion, considering that the vagus, for example, is 80 per cent sensory fibers (1). Such a concept is of the same pattern as that of more thoroughly studied regulatory mechanisms in which function of the part also gives rise to limiting reflexes. The relationship between baroreceptors and blood pressure, between respiration and pulmonary stretch receptors, and between stretch receptors and voluntary muscle activity could not be understood without reference to the sensory paths involved.

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‡ Associate Professor of Pharmacology and Assistant Clinical Professor of Medicine, University of California, San Francisco.

The thesis of this discussion is that motor activity of the smooth-muscle tubes is intrinsically activated and is independent of extrinsic parasympathetic innervation. Distention not only initiates the inherent activity but also gives rise to afferent (stretch) impulses which reach cord or brain-stem centers by pathways which may be anatomically associated with either the sympathetic or parasympathetic nerves. The activity generated by distention is limited by reflex sympathetic stimulation. Anatomic or pharmacologic denervation will yield varying results depending upon whether the afferent fibers from the organ are interrupted or remain intact, and upon whether the organ is distended or not.

The proposed concept can be established from information already in the literature. The information is summarized here as applied to several organs, particularly the bladder and intestine.

APPLICATION TO URINARY BLADDER

The applicability of the present thesis to the urinary bladder can be established if two stipulations are accepted. First, the discussion concerns the control of activity of the smooth muscle of the bladder wall and not the act of micturition or the reflexes governing it. Micturition involves predominantly voluntary muscle in its execution (2). Second, many of the effects on the bladder which follow nerve section or spinal cord injury are due to massive, prolonged distention with irreversible damage to the muscular wall. These changes, due to the atony attending spinal shock and to obstruction secondary to the loss of the micturition reflex are avoided when by catheterization or manual expression the distention is prevented (3, 4).

If these stipulations are accepted, it can be asserted with assurance that section of the parasympathetic supply to the bladder results ultimately in an increase in motor activity, not, as might be predicted and as many textbooks and discussions state, in paralysis.

Elliott (5) in 1907 observed that loss of the micturition reflex after pelvic nerve section led to bladder distention initially, but that the bladder regained tone, the muscular wall hypertrophied, and rhythmic contractions appeared as the bladder was distended. There have been many studies since, which confirmed the development of a contracted, irritable, hypertrophied bladder following pelvic nerve section (6, 7).

Pelvic nerve section interrupts those afferent fibers responding to distention and should not be referred to simply as parasympathetic denervation. Morphologic studies show (8) that after sacral sensory-root section, the muscle spindles disappear, as do all endings in the dome of the bladder. Physiologic studies (9) also establish that afferent fibers from the bladder wall do not course with the sympathetics.

If loss of sympathetic, inhibitory tone is the explanation for the bladder hyperactivity under discussion, sympathetic denervation should lead to equally intense changes. Although sympathetic nerve section does apparently lead to bladder hyperactivity, the magnitude of the change is not comparable to the results of pelvic nerve section (6, 7). This discrepancy is explained by the dif-

ficulty of achieving complete sympathectomy by surgical means, in this as well as other organs. Those investigators who cut only the hypogastric nerve do not interrupt the contribution from the third and fourth sacral paravertebral ganglia. More importantly, removal of the total ganglionated chain does not remove all of the ganglion cells. Groups of sympathetic ganglion cells (the intermediate ganglia) are common in the lower lumbar area. They may be on the gray rami, in the ventral roots, or near the attachment of the rami of spinal nerves. The postganglionic fibers from such cells mostly pursue a recurrent course into spinal nerves, and their preganglionic fibers reach them through associated ventral roots. Sympathetic ganglion cells are thus not all included in the pre- and paravertebral ganglia and are also not all thoracolumbar (10, 11). Since a single intact nerve root will maintain normal bladder function (12), these aberrant sympathetics are quantitatively important.

The more complete sympathectomy achieved by ganglionic blockade does lead to stimulation of the distended bladder, although blockade of the intrinsic ganglia will usually have the opposite effect (unpublished observations).

We know also from Elliott's work that complete denervation does not lead to a paralyzed bladder.

The central connections of the sympathetic inhibitory reflex generated by distention of the bladder have not been studied as directly as those from the intestine. However, the diffuse activation of sympathetic activity apparent in paraplegic patients during bladder distention allows inferences to be made concerning the nature of the cord connections of this reflex. In normal human subjects, distention of the bladder leads to vasoconstriction of the skin in segments corresponding to the sympathetic innervation of the bladder. In paraplegics, bladder distention causes sympathetic hyperactivity marked enough to elevate the blood pressure 40 mm. of Hg or more, and the rise in blood pressure is greater the higher the level of cord section (13–15). The autonomic hyperreflexia or, if an analogy may be suggested, spasticity associated with loss of suprasegmental inhibition is abolished by ganglionic blockade (16, 17).

APPLICATION TO INTESTINAL MOTILITY

The effect of vagal or splanchnic nerve section on intestinal motility (the fundus of the stomach and the pylorus are special cases discussed separately) can be formulated in the foregoing terms if one considers that, in contrast to the bladder, the intestinal afferent fibers course with the splanchnic nerves.

Splanchnic nerve section leads to an increase in intestinal motility (18) apparently proportional to the completeness of the sympathetic denervation. Spinal anesthesia is perhaps the most efficient sympathectomy. This augmentation of smooth-muscle activity is due to loss of sympathetic inhibitory tone but is *not* due to unopposed vagal effects. Vagal section does not relieve the hyperactivity and complete denervation leads to the most intense changes. Celiac ganglionectomy in the dog, for example, results in bloody diarrhea and ulceration of the stomach and upper gastro-intestinal tract (19). After denervation by nerve block in the mesentery, the intestinal segment subtended becomes maximally contracted (20).

Thus the results of vagal section itself are unimportant for our argument, since the vagus cannot be involved in the exaggerated activity of the denervated gut. However, the effects of vagal section may be summarized by saying that (the fundus of the stomach excepted) no decrease in motility is seen. Actually, there is some increase in motility, not marked except at the pylorus and in the rabbit. With the pyloric changes again excepted, this increase is probably secondary to delayed emptying of the stomach (18, 21).

In the case of the intestine, then, parasympathetic nerve section is without major effect, but sympathetic nerve section is followed by alterations in motility. It can be established from the many studies available that these changes in the degree of sympathetic control are generated by distention of the intestine and that the splanchnic nerves are the important afferent paths.

Central connections of the stretch reflex. The study of Chang and Hsu (22) on the localization of the intestinal inhibitory reflex arc is crucial to the present argument. Two unconnected loops of intestine were prepared. The motility of one loop was inhibited by distention of the other (or by electrical stimulation of a mesenteric nerve from the second loop). The inhibitory reflex persisted after vagotomy, adrenalectomy and cord section above T8. Splanchnic nerve section abolished the reflex. Nerve-root interruption experiments established that the afferent fibers enter by way of dorsal roots T7-L1 and that the efferent fibers leave from the same segments. There are many other studies in which the same conclusion is implicit, but none so complete.

The diffuse activation of the sympathetic nervous system by duodenal or rectal distention has been demonstrated by the occurrence of vasoconstriction in the hands and feet (23).

Effect of ganglionic blocking agents. Ganglionic blocking agents ordinarily cause an inhibition of the activity of the intestine, presumably by blocking conduction in the intrinsic ganglia. Under certain circumstances, however, administration of tetraethylammonium chloride or hexamethonium leads to an augmentation of motility before the inhibition appears (24–26). This stimulant effect appears only if the organ is distended (26) or if the peritoneal receptors are stimulated by laparotomy (unpublished observations). Stimulation does not appear if motility is recorded without laparotomy or luminal distention and is also prevented by splanchnic nerve block (26). The facts support the contention that distention not only initiates intestinal activity but that it (or peritoneal irritation) also initiates limiting, sympathetic reflexes. Moreover, an application to paralytic ileus is suggested.

Paralytic ileus. Peritoneal irritation, either by chemical or bacterial means, leads to adynamic ileus. In both experimental and clinical situations it has been shown that removal of the sympathetic inhibitory tone by splanchnic section or anesthesia, or by spinal anesthesia, leads to a return of intestinal motility (27–30).

APPLICATION TO OTHER ORGANS

The long-recognized lethal changes that follow denervation of the lungs have recently been restudied by Schmitt and Meyers (31), who investigated the acute

pulmonary edema that follows vagal section in the guinea pig. They concluded, on the basis of protecting and intensifying drug effects, that the changes in the lungs are due to afferent denervation and a resultant loss of sympathetic tone necessary for normal pulmonary function.

The uterus (intra partum and post partum) is also stimulated by removal of sympathetic influences, either by spinal anesthesia (32–34), paravertebral block (35), or hexamethonium (36). Relevant studies of afferent activity from the uterus other than pain transmission are not available.

The only evidence that the gall bladder is in any way similar to the other smooth-muscle sacs is the observation that hexamethonium causes it to contract (25).

Distention of arteries leads to a decrease of sympathetic tone, accomplishing the same limitation of response that distention of other hollow organs accomplishes by an increase in sympathetic activity. The arterial presso-receptors are concentrated in a few familiar areas but are also found in the mesenteric circulation (37, 38) and in the area of the descending aorta (39). Alexander (40) has shown that distention of veins also activates vagal afferent impulses which inhibit sympathetic outflow and lead to venous dilation.

DISCUSSION

The data reviewed here establish that section of the sympathetic and parasympathetic nerves to the intestine and urinary bladder does not lead to the changes predicted by the usual formulation of autonomic nervous system physiology. It no longer seems presumptuous, then, to discuss the probability that the whole concept of sympathetic-parasympathetic antagonism has very limited applicability.

First of all, many autonomically governed organs do not have a dual innervation. The nictitating membrane (41), most blood vessels, and the sweat glands (except possibly those in the cephalic area) (42) are supplied exclusively by sympathetic fibers. On the other hand, a sympathetic innervation to the lacrimal glands has never been demonstrated. The ciliary body, it is now acknowledged (43), is also governed entirely by the parasympathetic nerves. Even the reaction of the iridal muscle is controlled by changes in parasympathetic tone, the responses to changes in sympathetic tone being mediated by an entirely different effector—vascular smooth muscle (42, 44, 45). The salivary glands have both sympathetic and parasympathetic fibers entering them; but according to Babkin (46), a given cell type is innervated by one, but never both divisions. The compound glands can be more easily used to establish synergism rather than antagonism between the two divisions of the autonomic nervous system (47).

This is not to imply that the concept of intrinsic activity limited by sympathetic inhibition applies to each of the foregoing organs. Some of these organs do not have spontaneous activity, and most receive some motor influences from the central nervous system.

However, only the determination of cardiac rate is clearly subject to reciprocal inhibitory and stimulatory influences, and only changes in intrasinusal pressure

activate and inhibit the vagus and sympathetics in the expected manner. Other physiologic maneuvers inhibit only one division or cause simultaneous sympathetic and parasympathetic discharge (48).

In the development of the concept of reciprocal innervation of autonomic organs, experiments with the known mediators have been very influential. It is worth emphasizing that acetyl choline and epinephrine act on chronically denervated organs and on tissues devoid of nerves, either extrinsic or intrinsic. That acetyl choline acts on effectors such as the sweat glands or vascular smooth muscle does not prove that the same substance is released in these areas by extrinsic nerves, although it is highly suggestive of the source of intrinsic automaticity.

SUMMARY

The results of nerve-section experiments are inconsistent with the concept that the control of bladder and intestinal activity is through antagonistic effects of the sympathetic and parasympathetic nervous systems. The urinary bladder is not paralyzed but is rendered hyperactive by parasympathetic ("motor") denervation. Intestinal activity is augmented by sympathetic denervation, but this effect cannot be due to unopposed vagal influences, since vagal section does not alter the hyperactivity.

A more consistent explanation is derived by considering that sensory denervation removes the sympathetic inhibitory tone initiated by distention of the organ, that is, that activity is limited by the same stimulus that initiates it. Evidence that some other smooth-muscle organs are similarly governed is presented. The innervation of still other organs is such that the antagonism usually described cannot be accepted.

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PRELIMINARY CLINICAL OBSERVATIONS ON THE USE OF A BIGUANIDE (DBI) AS AN ORAL HYPOGLYCEMIC AGENT*

CHARLES WELLER, M.D. AND ALICE MACAULAY, M.D.

The Division of Internal Medicine and the Metabolic Clinic, Grasslands Hospital, Valhalla, N. Y.

Ever since parenteral control of diabetes mellitus was accomplished with the discovery of insulin, there has been an unremitting search for an effective oral substance as a substitute for insulin. It has been almost a third of a century since "Synthalin" (decamethylenediguanidine) was synthesized to treat diabetes. This substance was abandoned after careful studies, because of its toxicity (1). In 1942 Janbon and associates (2) were the first to demonstrate the hypoglycemic effect of a sulfanilamide derivative, IPTD. Loubatieres (3) and others studied this and related compounds. In 1955, 2 other sulfanilamides, carbutamide (BZ 55), and tolbutamide (Orinase), were studied in Germany by Bertram *et al.* (4), Franke and Fuchs (5) and others. These drugs have been studied extensively in this country (6, 7).

A non-sulfanilamide compound, N-beta-phenethylformamidinyliminourea (DBI), was found by Ungar *et al.* (8) to be a highly active oral hypoglycemic agent. They studied this substance in normal and alloxan-treated diabetic rats, rabbits, and monkeys. Early observations on DBI in man were reported by Williams (9) Pomeranze (10) and Krall (11) and their associates; they demonstrated a definite hypoglycemic effect.

The difference between the formula for DBI (a biguanide) and the formula for Synthalin (a diguanidine) is illustrated in Figure 1. Tolbutamide, a sulfonylurea is an entirely different compound. The methyl radical on the benzene ring is replaced with an amino radical to form carbutamide, a toxic compound.

Fajans and associates (12) reported that metabolic balance studies revealed no influence of DBI upon the excretion of nitrogen, potassium, 17-hydroxycorticoids or 17-ketosteroids in the urine. They observed that after administration of DBI there was a significant increase of blood pyruvate and lactate concentration, both in the fasting state and during glucose tolerance tests. Their results were consistent with the *in vitro* results of others which suggest that DBI produces hypoglycemia by increased anaerobic glycolysis. In diabetic patients there is no evidence that inhibition of adrenal function, decreased gluconeogenesis, or inactivation of glucagon activity are contributory factors. In significant contrast to the findings in animals, Fajans and co-workers observed no hypoglycemic effect of DBI in normal people. This is not in accordance with the observations of Pomeranze *et al.* (10). Skillman *et al.* (13) and others reported that the basal metabolic rate, serum protein-bound iodine level, thyroidal radioactive iodine uptake, and renal functions were unaltered by DBI. Ungar *et al.* (8) showed

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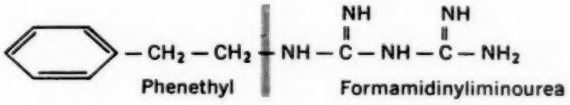
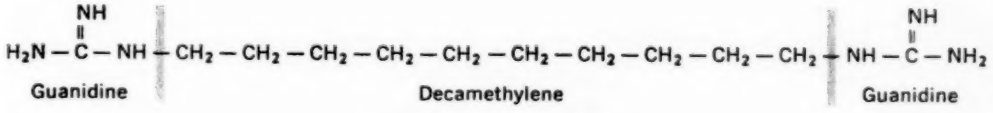
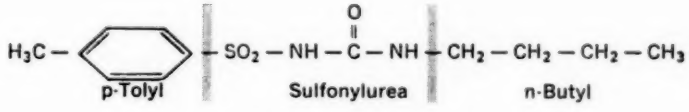


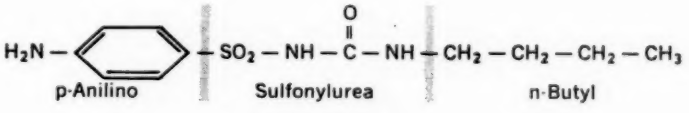
Phenethylformamidinyliminourea
(DBI)



Decamethylene diguanidine
(Synthalin)



1-n-Butyl-3-p-tolylsulfonylurea
(Tolbutamide)



1-n-Butyl-3-p-anilinosulfonylurea
(Carbutamide)

FIG. 1. Structural Formulas of Oral Hypoglycemic Agents

that a single dose of DBI will cause a gradual fall in the concentration of blood sugar, reaching maximal hypoglycemia between the fifth and sixth hours. The rise in the blood sugar level between the sixth and eighth hours occurs at a more rapid rate than the initial decline.

This report is a preliminary clinical observation on the use of DBI in diabetic patients. The patients were from a representative Diabetic Clinic population in a large county hospital.

MATERIALS AND METHODS

Forty-two patients with diabetes mellitus (average duration more than nine years) were studied for one to six months. Their ages ranged from 24 to 80 years. The diabetes could not

TABLE 1

Summary of All Diabetic Patients Treated with DBI

Patient					Duration of Diabetes	Type of Diabetes	Previous Rx	DBI Therapy		Other Drug with DBI	Results		
No.	Name	Age	Sex	Race				Duration	Max. daily dose (mg.)		Patient responsive without side-effects	Patient responsive with side-effects	Patient unresponsive or immediate nausea & vomiting
1.	C.A.	56	F	N	8 yrs.	Unstable	Insulin, 35 U.; Orinase	2 mos.	250	None	—	—	Yes
2.	W.A.	73	M	W	1 yr.	Stable	Insulin, 10 U.	6 mos.	125	None	Yes	—	Yes
3.	C.B.	50	M	N	3 mos.	Stable	Diet	3 mos.	100	None	Yes	—	—
4.	L.B.	73	M	W	3 mos.	Stable	Diet	3 mos.	100	None	Yes	—	—
5.	J.B.	72	F	N	6 yrs.	Stable	Insulin, 30 U.; Orinase	4½ mos.	125	None	—	Yes	—
6.	C.C.	69	F	W	12 yrs.	Stable	Insulin, 25 U.; Orinase	1½ mos.	150	None	—	—	Yes
7.	I.D.	70	M	W	5 yrs.	Stable	Insulin, 30 U.; Orinase	3 mos.	150	None	—	—	Yes
8.	F.D.	46	F	W	3 yrs.	Stable	Insulin, 20 U.	3 mos.	150	None	Yes	—	—
9.	F.deG.	53	M	W	2 yrs.	Stable	Insulin, 25 U.	5 mos.	50	None	Yes	—	—
10.	O.D.	63	M	N	1 mo.	Stable	Insulin, 15 U.	6 mos.	100	None	Yes	—	—
11.	F.F.	49	M	W	16 yrs.	Unstable	Insulin, 25 U.	2 mos.	125	None	Yes	—	—
12.	C.F.	78	M	W	7 yrs.	Stable	Insulin, 15 U.	6 mos.	125	None	Yes	—	—
13.	N.G.	76	M	N	15 yrs.	Unstable	Insulin, 20 U.	7 days	150	None	—	—	Yes
14.	C.N.	49	F	W	3 mos.	Unstable	Insulin, 35 U.	3 wks.	200	None	—	—	Yes
15.	P.J.	61	F	W	5 yrs.	Stable	Insulin, 10 U.; Orinase	4 mos.	75	None	Yes	—	—
16.	E.J.	38	F	N	26 yrs.	Unstable	Insulin 40 U.	3 days	75	None	—	—	Yes
17.	R.J.	57	F	N	10 yrs.	Unstable	Insulin, 35–50 U.; Orinase	6 mos.	200	None	Yes	—	—
18.	E.L.	64	F	N	22 yrs.	Stable	Insulin, 30 U.	1 mo.	75	None	—	Yes	—
19.	A.M.	66	F	N	12 yrs.	Unstable	Insulin, 25 U.; Orinase	6 mos.	175	None	—	—	Yes
20.	S.M.	25	M	W	5 yrs.	Unstable	Insulin, 105 U.	2½ wks.	275	NPH, 20 U.	Yes	—	—
21.	L.N.	69	F	W	1 yr.	Unstable	Orinase	4½ mos.	275	None	—	—	Yes
22.	M.N.	57	F	W	7 yrs.	Unstable	Insulin, 35 U.; Orinase	3 mos.	150	None	Yes	—	—
23.	E.P.	45	M	N	9 yrs.	Unstable	Insulin, 80 U.	6 mos.	300	NPH, 60 U.	Yes	—	—
24.	H.R.	80	M	W	44 yrs.	Stable	Diet	3 mos.	75	None	—	—	Yes

24.	H.R.	80	M	W	44 yrs.	Stable	Diet						
25.	J.R.	66	M	W	10 yrs.	Unstable	Insulin, 35 U.; Orinase	3 wks.	150	None	—	—	Yes
26.	A.R.	70	M	W	2 yrs.	Unstable	Insulin, 30 U.	3 wks.	75	None	—	—	Yes
27.	S.R.	53	M	W	15 yrs.	Unstable	Insulin, 65 U.	2 mos.	150	NPH, 30 U.	—	Yes	—
28.	M.R.	61	F	W	10 yrs.	Stable	Diet	3 mos.	82.5	None	Yes	—	—
29.	J.S.	64	M	N	1 yr.	Unstable	Insulin, 15 U.	5 mos.	125	None	Yes	—	—
30.	A.S.	63	M	N	15 yrs.	Unstable	Insulin, 15–70 U.	5 mos.	175	None	Yes	—	—
31.	W.S.	51	M	N	1 yr.	Stable	Insulin, 20 U.	3 mos.	75	None	Yes	—	—
32.	E.S.	55	F	N	3 yrs.	Unstable	Insulin, 10 U.	2 mos.	75	None	Yes	—	—
33.	H.S.	79	M	W	1 yr.	Stable	Insulin, 10 U.	3½ mos.	75	None	—	—	Yes
34.	L.S.	66	F	N	11 yrs.	Stable	Orinase	1 wk.	75	None	—	Yes	—
35.	Jo.S.	73	M	W	20 yrs.	Stable	Insulin, 35 U.	7 wks.	125	None	Yes	—	—
36.	Le.S.	54	F	W	20 yrs.	Stable	Insulin, 15 U.	2½ days	150	None	—	—	Yes
37.	M.S.	61	M	W	4 yrs.	Stable	Insulin, 30 U.	6 wks.	125	None	—	—	Yes
38.	L.T.	45	F	N	24 yrs.	Stable	Insulin, 25 U.	5 wks.	300	None	Yes	—	—
39.	E.W.	59	F	N	3 yrs.	Unstable	Insulin, 30 U.	3 mos.	150	None	Yes	—	—
40.	B.W.	76	F	N	18 yrs.	Unstable	Insulin, 15 U.; Orinase	1 wk.	75	None	—	Yes	—
41.	C.W.	51	F	N	13 yrs.	Unstable	Insulin, 80 U.	4 mos.	125	NPH 20 U.	Yes	—	—
42.	A.L.	20	F	W	4 yrs.	Unstable	Insulin, 60 U.	4 days	300	NPH, 40 U.	—	—	Yes

be controlled by diet alone and there was definite need for antidiabetic therapy. The patients with more severe and unstable diabetes were hospitalized, and those with milder disease were treated on an ambulatory basis. Blood sugar determinations made by the Somogyi modification of the Folin-Wu method. Fractional and 24-hour quantitative urine analyses were performed by the Benedict and Clinitest methods. Liver function tests, hematograms, and kidney function tests were carried out during a preliminary control period and again after DBI therapy.

If the patient was taking less than 20 units of insulin daily, or tolbutamide orally, the medication was discontinued until a rise in the blood sugar level or glycosuria occurred. If the dose of insulin was greater than 20 units, it was gradually lowered until glycosuria and hyperglycemia ensued.

DBI[1] was started with a dosage of 25 mg. three times a day with meals and slowly increased until normoglycemic blood levels were reached, or nausea and vomiting occurred. If meals were omitted, medication was also omitted. The dose of insulin was gradually lowered, and the dose of DBI was increased, until the desired blood sugar levels were established and/or glycosuria was controlled.

All patients were graded according to the following criteria:

A. *Responsive*

1. If the average blood sugar concentration was decreased by 30 per cent or more and/or if glycosuria was decreased by 50 per cent or more from levels achieved by previous therapy.
2. If the insulin requirement was decreased by 50 per cent or more.
3. If the response to DBI was equivalent to that achieved with previous therapy.

B. *Non-responsive*

Patients not fulfilling the foregoing criteria.

RESULTS

A summary of all patients treated with DBI is presented in Table 1. A summary of the responsive patients without side-effects (successful therapy) is shown in Table 2, which includes lists of previous insulin requirements and changes in body weight.

The results of DBI therapy in this group of diabetics were as follows:

A. Total responsive—27 patients (65 per cent).
   1. Responsive without side-effects (successful therapy)—22 patients (53 per cent).
   2. Responsive but with side-effects (nausea and/or vomiting)—5 patients (12 per cent).

B. Total non-responsive—15 patients (35 per cent).

It should be noted that the number of responsive patients exceeded the number in whom therapy was successful. In a few patients, satisfactory control of the diabetes was accompanied by such prominent side-effects that it was necessary to discontinue the otherwise effective drug.

[1] DBI was supplied through the courtesy of Dr. H. Sadow, U. S. Vitamin Corp.

TABLE 2

Patients Responsive to DBI, Without Side-Effects (22 Successful Cases)

Patient				Weight (lbs.)			Control of Symptoms	DBI-Hypoglycemic Effect (% fall)	DBI Hypoglycuric Effect of 50%	Insulin Requirement	
No.	Name	Age	Sex	Ideal	Actual	Change				Previous	With DBI
2.	W. A.	73	M	145	132	0	Yes	15	Yes	10 U.	0
3.	C. B.	50	M	158	160	+4	Yes	33	Yes	0	0
4.	L.B.	73	M	130	164	−6	Yes	22	Yes	0	0
8.	F.D.	46	F	133	154	0	Yes	30	Yes	20 U.	0
9.	F.deG	53	M	145	181	+4	Yes	0	Yes	25 U.	0
10.	O.D.	63	M	175	181	+5	Yes	42	Yes	15 U.	0
11.	F.F.	49	M	140	160	−3	Yes	15	Yes	25 U.	0
12.	C.F.	78	M	140	116	−10	Yes	31	Yes	15 U.	0
15.	P.J.	61	F	140	160	−12	Yes	8	Yes	10 U.	0
17.	R.J.	57	F	150	150	−7	Yes	42	Yes	35–50 U.	0
20.	S.M.	25	M	140	135	+5	Yes	30	Yes	105 U.	20 U.
22.	M.N.	57	F	140	177	−23	Yes	16	Yes	35 U.	0
23.	E.P.	45	M	180	168	+13	Yes	31	Yes	80 U.	60 U.
28.	M.R.	61	F	140	140	+6	Yes	16	Yes	0	0
29.	J.S.	64	M	150	126	0	Yes	38	Yes	15 U.	0
30.	A.S.	63	M	160	180	−11	Yes	0	Yes	35 U.	0
31.	W.S.	51	M	165	190	−13	Yes	23	Yes	20 U.	0
32.	M.S.	55	F	150	152	+3	Yes	40	Yes	10 U.	0
35.	J.S.	73	M	155	150	+5	Yes	0	Yes	35 U.	0
38.	L.T.	45	F	150	148	−10	Yes	0	Yes	25 U.	0
39.	E.W.	59	F	137	152	+2	Yes	40	Yes	30 U.	0
41.	C.W.	51	F	145	213	−24	Yes	0	Yes	80 U.	25 U.

TABLE 2A

Previous Insulin Requirements in 19 of the 22 Successful Cases
(DBI reduced requirement by 50% or more)

10–20 U.—9 patients (41%)
21–40 U.—7 patients (31%)
41–105 U.—3 patients (14%)

Three patients (14%) had not received insulin previously. Insulin was replaced completely in 16 patients—73%.

TABLE 2B

Weight Changes in 22 Successful Cases

No change— 3 patients (14%)
Gain — 8 patients (36%)
Loss —11 patients (50%)

(Weight loss beneficial in 6 of these 11 patients because of overweight.)

DISCUSSION

In applying these criteria to assess the efficacy of DBI, it was our purpose to determine not only whether DBI could replace insulin in some cases, but also to see whether it offered distinct advantages over insulin, other than in the mode of administration. Preliminary observations indicate that DBI is an effective oral preparation in the management of diabetes mellitus, not only in the older person with mild diabetes, but also in some patients with insulin-deficient diabetes. These include juvenile diabetics, adults with severe diabetes in whom larger doses of insulin are required, and patients with mild diabetes who fail to respond to other oral hypoglycemic therapy. We observed the desired 30 per cent minimum hypoglycemic effect in 46 per cent of the responsive patients, and the minimum hypoglycuric effect in all of them. DBI replaced exogenous insulin completely in 73 per cent of the 22 patients in whom DBI therapy was successful.

The mechanism of action of DBI is unknown at present.

In our series we did not find any evidence of toxic effects referable to the liver, hematopoietic system, kidney, pancreas or other organs. Two patients, while taking DBI, died of diseases not referable to diabetes; autopsies failed to reveal any evidence of toxic effects due to DBI. Nausea and vomiting occurred in 47 per cent of the patients. These symptoms usually developed several days after starting the drug, but sometimes they occurred after several weeks of therapy. Various drugs, including anticholinergics, antacids, and antihistaminics have been used concomitantly with DBI, without effect. The cause of the nausea and vomiting is unknown, but it is probably a central rather than a local effect. Most patients who experienced these side-effects were taking 75 to 150 mg. of the drug daily; in a few, reactions occurred only with the higher dosage. Reactions did not seem to be related to the patient's age or the duration or severity of the diabetes.

In some patients, a metallic taste and/or suppression of appetite became apparent. This frequently was the forerunner of nausea and vomiting. Some of these patients lost weight, possibly due to the side-effect. However, others who were taking DBI underwent no change in weight (14 per cent). Increased appetite was reported by some patients, and 8 of the 22 responsive ones (36 per cent) actually gained weight; as they were mostly thin individuals, the effect was desirable. In 2 well controlled cases, the patients alleged they had complete relief from the nervousness they had experienced while taking insulin; however, this nervousness may have been due to excessive insulin dosage.

Three patients, treated with both insulin and DBI, were able to lower their insulin dosage, and the diabetes appeared more stable (Table 2, Nos. 20, 23 and 41). One of these 3 was a boy who had severe diabetes. With the addition of DBI, his insulin dosage was reduced from 105 units to 20 units daily. There was marked improvement in control and stability of the diabetes, but insulin could not be discontinued completely. It is in this group of diabetics that DBI may be a useful supplement to insulin therapy.

Another group of patients is now being treated with a combination of DBI and tolbutamide. To date there have been no apparent synergistic effects.

SUMMARY AND CONCLUSIONS

A new drug, DBI, has been studied as a hypoglycemic agent in 42 unselected diabetic patients, for periods ranging from one to six months. By our criteria it was found to be effective in 53 per cent of the patients treated; it lowered the blood sugar level by 30 per cent or more in 46 per cent of the responsive patients. It was also found to be effective and have a stabilizing influence in diabetics who required large doses of insulin; their insulin dosage could be reduced by at least 50 per cent, though none could discontinue it.

The chief side-effect was nausea and vomiting, which occurred mainly with higher dosage. Five patients (12 per cent) who could not tolerate the drug responded favorably otherwise, but they were not considered "successful" cases.

No organic toxic effects were noted.

In managing the diabetic patient, the physician may be likened to the busy juggler with many objects in the air. In diabetes, constant dietary, emotional and physical adjustments must be made, all in relationship to therapeutics old and new, including insulin, the sulfonylureas, and now DBI. Although the addition of DBI may make the task more difficult in the beginning, it is apparent that DBI widens the spectrum of regulatory agents and has a significant place in the treatment of diabetes.

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RADIATION TREATMENT OF CANCER*

L. HENRY GARLAND, M.B.†

Department of Radiology, Stanford University Medical School Service, San Francisco Hospital, San Francisco, California

Conclusions as to the value of any therapeutic procedure in patients with cancer are subject to some degree of error because of variability in the natural course of the disease, the latent nature of microscopic metastases, and the frequent difficulty of measuring objective regression. Even when undisputed disappearance or regression of the tumor does occur, it is sometimes debated whether this is due to the treatment employed, to the natural course of the disease, to associated therapy, or even to the late effects of prior treatment. Subjective improvement is a treacherous yardstick; every experienced physician knows that kindness plus some new placebo is frequently followed by relief of pain, an increase in appetite and weight, and associated clinical improvement. At the present time, it is the consensus among oncologists that the evaluation of therapeutic methods must be made deliberately, after the passage of several years, and in the light of the known history of the disease. This need for the elapse of several years following the introduction of any new radiotherapeutic, surgical or medical procedure is all too often forgotten.

I should like to emphasize two points at the outset: 1) cancer in general is a disease, the control of which calls for prevention rather than treatment, and 2) current methods of curative treatment are essentially destructive or ablative and therefore leave much to be desired. Nevertheless, until prevention becomes applicable, treatment must command our earnest consideration.

The 2 methods most useful for cure are surgery and radiotherapy; the methods most useful for palliation are radiotherapy, surgery and chemotherapy. In this review, I shall attempt to summarize the present indications for, and results of, radiotherapy.

GENERAL PRINCIPLES

It is assumed that the following basic steps have been taken: (a) *Microscopic verification* of the type of tumor present and estimation of its degree of anaplasia. A well-differentiated tumor is commonly classified as Grade 1, an undifferentiated one as Grade 4, and tumors of intervening types as Grade 2 or 3.

(b) *Clinical classification of the extent of spread.* This may involve radiographic and other studies. Lesions still localized to a small area of the tissue of origin are classified as Stage I; lesions with local spread, as Stages II and III; and lesions with distant metastases, as Stage IV. This classification at best is imprecise, but is a useful guide in prognosis and the planning of treatment.

(c) *General clinical status of the patient.* Patients in poor general state, or of

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† Clinical Professor of Radiology.

very advanced age may need treatment for the underlying condition rather than for any cancer they happen to bear.

After obtaining the foregoing data, the more common tumors can be considered in two broad groups—the accessible and the inaccessible.

Accessible tumors include those of the skin, lip and oral cavity, larynx, breast, uterus and rectum. These constitute almost 50 per cent of all cases of cancer, and include the majority of tumors most readily diagnosable and curable.

The *inaccessible* group includes chiefly tumors of the stomach, colon, bronchus, prostate, bladder and ovary, and the lymphoblastomas.

In the first group, radical radiotherapy is often indicated for cure (except in rectal lesions); in the second, it is often indicated for palliation (except in gastric and colonic lesions) (1, 2). Lesions of the osseous and central nervous systems, and primary soft-tissue tumors are in another category.

METHODS OF RADIOTHERAPY

Effective radiotherapy depends on the deliverance of a curative or palliative dose to the involved tissue, in accordance with the problem at hand. With suitable, localized, accessible cancers, radical radiotherapy is indicated; with a few widely spread lesions (*e.g.*, medulloblastoma) it may also be indicated; with most cases of nonlocalized disease the plan is usually palliative. The indication for treatment does *not* depend primarily on the histologic estimate of radiosensitivity. Tumor radiosensitivity is a complex phenomenon, depending on several factors such as the cell type, the local blood supply, the degree of infection, and so forth. It cannot be predicted with the microscope, and is not synonymous with radiocurability. Some comparatively resistant tumors (resistant in the sense of requiring large doses of radiation to cause disappearance of cancer cells) are radiocurable, whereas some radiosensitive tumors are not. Radiocurability depends on such factors as the anatomic extent of disease, the type of tumor, the tolerance of adjacent structures, and the degree of natural drainage.

Choice of radiation source. Clinical radiotherapy may be performed with a wide choice of ionizing beams. In this brief summary no attempt will be made to cover all the modalities currently available, but certain points will be stressed. Most roentgen therapy, and perhaps 98 per cent of therapy for cancer, can be effectively delivered with 200 KV (that is orthovoltage) roentgen beams. Supervoltage or megavoltage beams (1,000 to 10,000 KV) are useful in a small percentage of cases, notably for deep-seated tumors in the extremely obese or in persons with cutaneous injury overlying the tumor. For certain cancers of the tongue, the maxillary antrum, and the cervix and corpus uteri, intracavitary or interstitial radium is desirable. (Gamma rays from cobalt and other artificial radioactive substances may be used as a substitute for radium, but without any particular advantage.) Radioactive isotopes have a small place in radiotherapy, notably in functional cancers of the thyroid gland.

The fact that orthovoltage roentgen therapy permits effective radiation of deep-seated tumors may be readily appreciated by studying depth-dose charts. The skin was once considered to be the limiting factor in radiotherapy. However,

under ordinary conditions of practice, and with patients of average build, one can deliver more orthovoltage radiation to the depth than the normal deep tissues will tolerate, without serious injury to the overlying skin (3). The relative biologic effectiveness of megavoltage beams (whether from linear accelerators, cobalt teletherapy units, or other machines) is about 75 per cent of that of 200 KV radiation as ordinarily measured (4). In other words, to equate the biologic effect of 200 KV radiation it is necessary to increase the megavoltage dose approximately one-third. When this is done, in radical cancer therapy, it will be found that subcutaneous, osseous and chondral changes are about equal with the 2 modalities.

Modifications of radiation beam by rotation (of tube or patient), by special motion (convergence and pendulum technique), by limitation (perforated lead grids and wedge filters), and by other devices have been tried, without significant improvement in most tumor areas (5). Cobalt^{60} teletherapy is essentially another form of megavoltage x-ray therapy. "The secret of cure" reported Ralston Paterson at the Southern California Radiological meeting in 1958 "lies not in the machine. Good treatment with old plants is better and less dangerous than haphazard treatment with new apparatus."

An evaluation of orthovoltage (200 KV) radiation in the therapy of cancer is shown in Table 1.

Cancericidal dose. Biologic effect depends on the dose absorbed, the tissue treated, the volume irradiated and the time during which the treatment is given. The exposure dose in air is measured in *roentgens* (r), whereas the absorbed dose in the tissues is estimated in absorbed roentgens (*rads*). With orthovoltage, 1 r absorbed in soft tissue equals 1 rad. Time of exposure (in hours or days), and area exposed (or volume) are necessary to calculate the biologic effect. For example, the following different doses will yield a comparable cancericidal effect in superficial tumors[1]:

Rads	Time	Area
2250	1 day	4 cm. diameter
4000	6 days	4 cm. diameter
6000	28 days	4 cm. diameter

However, the injury to the surrounding normal tissues (the tumor bed) will be least with the protracted exposure, because the recovery rate of normal cells usually exceeds that of neoplastic cells.

Translation of exposure dose into absorbed dose varies with the density of the tissue, is not simple, and will not be considered further in this paper.

The influence of field size on tissue tolerance is considerable. The foregoing doses would not be tolerated by large volumes, *e.g.*, those subtending a field 10 x 15 cm. The dose to such volumes must be reduced accordingly—sometimes to a degree negating cancericidal effect.

Colleagues in surgery and medicine are sometimes impatient with lengthy ex-

[1] Using orthovoltage beams with half-value layers of 0.5-mm. to 2.0-mm. copper.

TABLE 1

Advantages and Disadvantages of Orthovoltage (200 KV) Radiation in Cancer

Advantages

1. Less damage to deeper normal structures. (All radiations damage normal tissues to some degree. Since proportionately more megavoltage rays reach the depth, and affect the normal tissues adjacent to a tumor, orthovoltage beams can be less injurious to deep structures.)
2. Less sharpness of beam edge at tumor depth: wider beams are used. (Most deep seated tumors are *not* well circumscribed; infiltration and lymphatic permeation eliminate such. Even with small tumors like retinoblastomas, the best published five-year results have been obtained with 200 KV) (6).
3. Earlier indication of tolerance level. (Skin erythema is a useful clinical indicator of tissue tolerance. When absent, as with megavoltage, serious late subcutaneous injury and fibrosis may develop unexpectedly (7). Spinal cord and brain damage are more apt to occur with megavoltage; pulmonary fibrosis is as frequent (8). For persons of average build, skin tolerance is *not* the main limiting factor in radiotherapy; it is intestinal and bronchial epithelial tolerance.)
4. Beam adjustment easier. (Flexible orthovoltage tube cones can be aimed more easily and accurately at certain tumors.)
5. Rotation therapy more feasible. (The best rotation-therapy results published to date have been obtained with 200 KV) (9).
6. Relative biologic effect superior (4). (As ordinarily measured, the biologic effectiveness of the megavoltage roentgen is less than that of the orthovoltage roentgen by a factor of about 0.75. When the megavolt dose is increased by one-third (to equate the orthovolt dose) such reactions as radiation sickness, bone necrosis and other side-effects tend to be of similar magnitude. There is no valid evidence that megavoltage produces better cure or palliation (3, 7, 10–12). The early skin reactions with orthovoltage, though severe, are reported to be better tolerated than the late subcutaneous reactions with megavoltage (7, 11).
7. Wide availability. (Megavoltage therapy has also been available in some areas for 30 years.)

Disadvantages

1. Decreased and potentially inadequate depth dose in very obese patients.
2. Inadequate cancericidal dose in lesions lying beneath previously injured skin.
3. Simplicity. (We tend to be more impressed with "super" apparatus.)
4. Lack of novelty. (We tend to seek potentially "new" radiations.)

pressions of radiation dose, but without them the data mean little or nothing. Correct calculation and application of the dose is time-consuming, fairly complex and may require the aid of the radiation physicist. Judicious adjustment of daily dose to the condition or reaction of the individual patient can spell the difference between failure and success in clinical therapy. Whereas a radical approach may be called for in curable cases of accessible cancer, a moderate or gentle dose may be the most effective in such conditions as reticulum-cell sarcoma and chronic leukemia.

SELECTION OF CASES

Radiation therapy is useful for *cure* in the following specific types of cancer: cancer of the skin, lip, oral cavity, larynx, cervix, and corpus uteri. It is sometimes useful for cure in selected cases of reticulum-cell sarcoma, medulloblastoma,

and Wilms' tumor. It is productive of apparent cure or long-term arrest in selected cases of breast cancer.

It is useful for *palliation* in the large group of primarily inaccessible tumors (notably those of the brain, bronchus, kidney and bladder), in the lymphoblastomas, and in selected cases of inoperable, recurrent or metastatic cancer. The large group of cancers of the intestinal tract, notably those of the stomach and colon, is unfortunately not particularly radiocurable. However, there is no uniformly reliable method of assessing the radiocurability of a tumor other than by studying its behavior in the patient under treatment.

Since surgical removal of localized tumors is a long-established and effective mode of treatment, the question may be asked "what are the advantages of radiation therapy"? We believe these may be summarized as follows:

1. Better cosmetic results (notably in cancer of the skin about the mouth and eyelids).
2. Better functional results (notably in cancer of the lip, tongue and larynx).
3. Better clinical results (notably in cancer of the cervix uteri, Hodgkin's disease, lymphosarcoma and medulloblastoma).
4. Less physical stress on some patients in poor general condition (for example, cancer of the fundus uteri in a patient with severe hypertension).

The disadvantages of radiation therapy include late atrophy, fibrosis, and occasionally neoplastic metaplasia. Meticulous individualization of technique tends to reduce these to a minimum.

The types of tumor listed as suitable for radiotherapy in this article reflect, in general, the established policy of the Stanford University Service at the San Francisco Hospital—a policy evolved in joint conferences of staff surgeons, radiologists and pathologists, aided in appropriate instances, by specialists in other disciplines. It has been described elsewhere in greater detail (1, 2, 13).

RESULTS

Satisfactory results in radical radiotherapy for cancer are measured in terms of destruction of the tumor; in palliative radiotherapy they are measured by relief of certain subjective or objective evidence of tumor. Results depend on the type and stage of the disease, the age of the patient, and the treatment given. They are calculated from the date of completion of definitive radiotherapy. The five-year yardstick is a useful criterion for the trend in results but is not by any means a perfect measure. When five-year results are based on all cases seen with a particular type of cancer, they are termed *absolute*; when they are based on all cases treated, they are termed *relative*. The latter figures may be further modified by excluding from calculation those patients dying of intercurrent disease prior to the expiration of five years; the results are then termed *determinate*. In mammary cancer, for example, an absolute survival rate of 35 per cent may be the same as a relative survival rate of 50 per cent, and a determinate survival rate of 55 per cent. Since it is not always possible to be certain that there is no residual disease, the term survival is usually preferable to the term cure. but admittedly it includes some patients with known residual disease. For instance, continuing with the foregoing sample of mammary cancer, the relative

cure rate under the hypothetical circumstances might be 40 per cent. These widely different percentages all refer to exactly the same number of patients.

Cancers in Accessible Sites

Skin. Curative radiotherapy requires the deliverance of enough irradiation to destroy or alter permanently the tumor cells, with maximal sparing of adjacent normal tissues. This may be achieved by judicious choice of beam quality, distance and technique. Carcinomas arising in regions of the body which tolerate heavy radiation poorly (dorsum of the hand, sole of the foot, large lesions involving the ear, and large lesions of the skin of elderly patients in pressure sites such as the occiput or buttocks) should be treated with great care, or by surgery. If there is clinical evidence of regional lymph-node involvement, surgical removal of operable nodes is usually indicated (after control of the primary lesion). If the nodes appear to be inoperable, irradiation will provide temporary control in a fair number of cases and permanent arrest in a few.

Our experience[2] encompasses over 900 cases[3]. The five-year cure rate in small lesions (Stages I and II) is about 95 per cent; in more advanced lesions (Stages III and IV) it is considerably less (14).

A small percentage of skin cancers may recur after apparently adequate irradiation or surgery. Marginal recurrences can be successfully re-treated by irradiation in selected cases; central recurrences should usually be treated by surgery. Low voltage and orthovoltage roentgen therapy are the agents of choice.

In the majority of basal-cell and squamous-cell skin cancers, the cosmetic and functional results of correctly used radiotherapy are superior to those obtainable by other treatment. Needless to say, some very small lesions can be cured by the simple excision required for biopsy, and some extremely advanced lesions (with secondary infection and bone involvement) may be best handled by radical surgery. Between these two extremes lie the majority of cases; and, in these, irradiation is considered to be the method of choice.

Space does not permit consideration of the problem of malignant melanoma.

Lip. The optimal treatment of most cases of cancer of the lip is fractionated roentgen therapy. Daily doses of 200 to 500 rads up to a tumor dose of from 4 to 6000 rads in from two to four weeks tends to result in cure with the least telangiectasis and atrophy. Our experience includes over 200 cases. The five-year cure rate is approximately 90 per cent for small lesions, and proportionately less for more advanced lesions, especially those with metastases to the lymph nodes. Our recurrence rate after radiotherapy is approximately 7 per cent. Our incidence of known subsequent lymph node involvement is less than 10 per cent. The latter cases are recommended for radical surgery when they appear to be operable, and for radiotherapy when unoperable.

In 1950 we reported five-year results in 121 cases: the overall five-year cure rate was 80 per cent, but when nodes were involved it fell to 25 per cent (14).

Oral cavity. Cancers of the oral cavity include cancers of the tongue, floor of

[2] Drs. Garland, Hill, Mottram, Sisson and Heald.

[3] Seen on the Stanford University Service at the San Francisco Hospital, at St. Joseph's Hospital, and in private office practice.

mouth, palate, cheek, alveolar ridges and fauces. Most localized tumors not over about 2 cm. in diameter can be well treated by radical radiotherapy and, with the exception of the tongue, have a high cure rate (about 75 per cent). More advanced lesions, or those with metastases, have a correspondingly smaller chance of cure and require variable combinations of external roentgen therapy, interstitial radium therapy and surgery—or radical surgery alone. Our five-year survival rate in 71 cases of cancer of the tongue reported some years ago was: for lesions in the anterior two-thirds, without nodes, 50 per cent; with nodes, 15 per cent. For lesions in the posterior third there were no cures (14). Our series now includes several ten-year cures of cancers of the floor of the mouth, palate, cheek and tonsil.

Larynx. Our experience with laryngeal carcinomas exceeds 160 cases. Of these, 100 were treated five or more years prior to this report. The majority of them were intrinsic tumors: the five-year determinate survival rates for patients in this group are as follows:

Stage I (single cord, without fixation).....88 per cent.
Stage II (both cords or one cord with partial fixation).....79 per cent.
Stage III (one or both cords, with invasion or metastases).....33 per cent.

Some of the patients who were not cured by radical radiotherapy had subsequent laryngectomies, with arrest of the disease. A single, correctly given course of radiotherapy does not, according to many of the surgeons with whom we have had the privilege of working, make the subsequent surgery more difficult. The reason for this is that the surgeon (in performing radical laryngectomy) is working outside the field of prior radiotherapy. It is a totally different matter when surgery is attempted after wide-field radical or intermittent roentgen therapy, especially in the presence of infection.

The five-year arrest rate in the entire intrinsic group was 46 per cent (absolute) and 58 per cent (determinate). In the extrinsic group it was much less satisfactory (15, 16).

Breast. Our policy for treatment of carcinoma of the breast has been published elsewhere in detail (17, 18). Suffice it to say that when the tumor is confined to the breast itself, simple mastectomy is adequate for cure. When the tumor has spread beyond the breast, in the great majority of cases there is lymphatic extension to areas not removable by standard radical surgery and also vascular spread to an extent that explains the great tendency of the disease to manifest itself as recurrent or metastatic in years to come. Therefore, a sound program for most cases of primary mammary carcinoma is that bearing the name of McWhirter, consisting of simple mastectomy followed by radical radiotherapy to the regional lymphatic areas in the chest wall, axilla, supraclavicular and upper anterior mediastinal areas. Using this method, five-year absolute survival rates can be obtained which are, if anything, slightly superior to those reported by the use of radical surgery, and the degree of morbidity from extensive scars of the chest wall or edema of the arm is less. Should radical radiotherapy be contraindicated in primary cases, there is no question that radical mastectomy is the best alternate method for treatment. The prevalence of chest-wall recurrence and

regional lymphadenopathy is distinctly less after radical than after simple operation without radiotherapy.

When radical mastectomy has been used as the primary approach, and microscopic evidence of tumor is found in the removed nodes, postoperative radiotherapy to the regional nodal areas (but not the chest wall) is advisable.

We now have 65 cases treated by simple mastectomy and radical postoperative radiotherapy. The five-year survival rate for tumors in all stages combined was 51 per cent; in those classified as Stages I and II it was 67 per cent.

Our experience with radiotherapy following radical mastectomy covers over 600 cases. The five-year results were in the usual range (*i.e.*, about 72 per cent in cases "without nodes," and 30 per cent in cases with axillary nodes).

Uterine cervix. The simplest clinical classification of cervical cancer is that of the League of Nations, Stage I being a lesion confined to the cervix itself, Stage II a lesion extending to adjacent structures but not invading the pelvic wall or floor, Stage III a cancer involving the pelvic wall or floor, and Stage IV a tumor invading the bladder, rectum or distant structures. The variation in proportion of cases in the different stages in different clinics is considerable. Partly because of this fact, combined five-year results obtained at one clinic may not be comparable with those obtained at another.

Our experience with invasive cancer of the cervix exceeds 550 cases. The approximate five-year survival rates in recent decades were: Stage I, 75 per cent; Stage II, 40 per cent; Stage III, 32 per cent; and Stage IV, 9 per cent. The overall five-year survival rate in treated cases at the San Francisco Hospital was 44 per cent and at St. Joseph's Hospital, 49 per cent.

These results were obtained with a combination of external roentgen irradiation plus intracavity radium therapy, using the "Stockholm" technique. In general, we recommend that the external therapy precede the radium therapy, except in Stage I[4]. There are many different methods of delivering the radiotherapy to the pelvis, but despite these variations, the five-year results in different radiological centers are quite similar. It is important to note that with orthovoltage (200 KV) one can usually deliver more radiation to the pelvic structures than the normal rectal wall, bladder or small-bowel will tolerate, and yet avoid permanent severe injury to the skin. Therefore, except in extremely obese patients, orthovoltage therapy and suitable radium applicators may be used for best results. It is essential to check the precise position of the radium applicators after insertion and prior to removal. When this is done, and necessary corrections made in placement, the incidence of rectal damage will be minimal. The early and late reactions to improperly applied radical pelvic irradiation are serious. It is therefore of the greatest importance that patients be treated by those who have had adequate training and experience in the use of these powerful agents. Despite the most careful attention to details, in about 7 per cent of cases late complications will occur: these include rectal ulceration, small-bowel or sigmoid stricture, and fracture of the femoral neck. This percentage is an acceptable hazard in the light of the radiocurability of the disease. (It is actually lower than the incidence

[4] Carcinoma in situ is probably best treated by surgery.

of ureteral necrosis and other complications following radical surgery, reported by Meigs as 10 per cent.)

As many gynecologists have noted, there is a potential small mortality risk and a certain incidence of annoying complications from irradiation, yet this form of therapy remains the best treatment of cancer of the cervix. There are no large-series surgical results to equal it (19).

Radiotherapy of advanced pelvic cancer can often accomplish much worthwhile palliation (20). The immediate post-therapeutic morbidity tends to be considerably shorter than that resulting from pelvic exenteration, and the period of survival tends to be more tolerable and certainly much less of a burden on friends and relatives.

The corpus uteri. The optimum treatment for cancer in this area depends upon its stage. We recommend preoperative radiotherapy (usually by multiple intracavitary radium sources) followed after six weeks by radical hysterectomy. Some believe that in the earlier stages of the disease, hysterectomy alone will give comparable results. In clinically inoperable cases, five-year arrests have been obtained in over 50 per cent, by radiotherapy alone.

Rectum. The best treatment is radical surgery. For borderline operable cases, some recommend combined preoperative roentgen therapy and radical surgery. For frankly inoperable cases external roentgen therapy supplemented by intracavitary or interstitial radium may be helpful. The occasional value of radiation is exemplified by 2 patients with large inoperable cancers reported by Brindley and White: these were treated by simple colostomy, followed by vigorous local radiotherapy. Both are well and apparently free of disease over nine years following treatment. These results are mentioned, not to encourage radiotherapy of operable lesions, but to remind you that it is sometimes useful in inoperable ones.

Cancers in Inaccessible Sites

Primary bronchial carcinomas. The best treatment of operable bronchial cancer is surgery. Unfortunately, most cases are still diagnosed when the tumor is no longer entirely removable. In selected cases with inoperable tumors, radiotherapy is of considerable value in reducing symptoms and occasionally in prolonging life. Tumor doses of about 3000 rads, orthovoltage, given over a period of three or four weeks will permit palliation in most instances. Tumor doses of 5000 to 6000 rads over four to six weeks will occasionally be curative. In a review of several hundred cases of untreated primary bronchial cancer we found that the median duration of life was 3.5 months after diagnosis, and in treated cases approximately 7 months. An occasional five-year survivor was observed (10, 21).

Metastatic pulmonary tumors of radiosensitive nature (from testis, ovary and breast tumors, neuroblastoma, and Ewing's sarcoma) are frequently worth treating, as good temporary control may ensue.

Esophagus. The palliative results of radiotherapy of carcinoma of the esophagus are modest. Nevertheless, this treatment represents one of the few definitive nonsurgical measures currently applicable for many of these patients, and therefore should be utilized when possible.

TABLE 2

Leukemia and Lymphoblastoma.
*Recommended Treatment Program**

Disease	Surgery	Radio-therapy	Chemotherapy
Leukemia			
Acute lymphoblastic	—	—	Steroids†
Acute myeloblastic	—	—	? 6-Mercaptopurine†
Chronic lymphocytic	—	+	(Chlorambucil, terminally)
Chronic myelocytic	—	+	(Myleran, terminally)
Hodgkin's Disease			
Localized	?	+	—
Multiple areas	—	+	—
Generalized	—	+	(Nitrogen mustard, alternating with, or augmenting x-ray therapy, terminally)
Lymphosarcoma			
Localized, bowel	+	—	—
Localized, other	—	+	—
Multiple areas	—	+	—
Generalized	—	+	—
Reticulum-cell sarcoma	—	+	—

* When treatment is indicated. Some "benign chronic" cases may need only periodic observation. Some terminal cases may need combined therapy.

† Radiotherapy occasionally for large local masses, or intracranial lesions.

Other sites. Space does not permit consideration of results in the treatment of other inaccessible tumors, notably those of the central nervous system, osseous system, genito-urinary tract, nasal accessory sinuses, eye, parotid and thyroid gland (22). In a few of these sites, curative radiotherapy is sometimes possible (*e.g.*, medulloblastoma, Wilm's tumor, solitary bone neoplasm and cancer of the bladder); in others, palliative treatment may be effective.

Our policy with the lymphoblastoma-leukemia group is summarized in Table 2. These neoplasms are particularly susceptible to roentgen therapy because this agent is the more easily "titrated" form of radiation, has fewer side-effects than chemotherapy and is more generally available.

REASONS FOR FAILURE OF RADIATION TREATMENT

The reasons for failure in radiotherapy are similar to many of those applicable to any form of therapy, including surgery. They embody conditions pertaining to the tumor and conditions pertaining to the host:

Local reasons:

A. Extremely extensive tumor.
B. Tumor that has already metastasized.
C. Inadequate technique (size of field too small, dose too low or too high, protraction too great, or fractionation too unequal).
D. Radio-resistant tumor (a phenomenon more apt to be observed after previous inadequate radiotherapy).

Host:

A. Feeble or terminal patient with little recuperative power.
B. Badly infected tumor, or tumor in patient with severe anemia.
C. Unreliable or uncooperative patient who attends irregularly.
D. Intercurrent disease, including various vascular and systemic disorders, expecially in the aged.

Failure, therefore, is seldom dependent primarily on the facilities available. This is illustrated by the so-called "60–30–10" law of factors influencing radiologic curability: about 60 per cent depends upon the type and extent of the tumor, about 30 per cent depends upon the skill and experience of the therapist, and about 10 per cent depends upon the modality employed.

SUMMARY

Radiation therapy has an important role in the curative treatment of cancer, and a useful role in palliation. It should be combined with periodic follow-up of all cases. The basic principle in curative therapy is the eradication of tumor without irreparable damage to adjacent structures.

The principal limiting factors in radiologic cure of cancer are biologic, not physical. These are 1) the type and extent of the tumor, 2) the status of the tumor bed, and 3) the status of the host. All these factors influence the outcome more than does the type of voltage or equipment employed.

Effective radiation can be administered in the majority of cases with orthovoltage beams or with a judicious combination of x-rays and radium. Megavoltage beams are useful with extremely obese or heavy patients, but have not yielded superior palliation or cure rates.

The skin is not the limiting factor in adequate dosage of deep-seated curable tumors; 200 KV beams can destroy bowel or bronchial epithelium without irreparable skin damage. The relative sensitivities of the tumor and its tissue bed are of much more importance than the voltage employed.

The results obtained in a series of selected types of cancer treated with radiotherapy are summarized.

Radiotherapy is widely available in this country today, and should be utilized more extensively in the care of cancer. This will be aided if the radiologic management of cancer is accorded some of the tremendous amount of time currently devoted to surgical management in undergraduate and graduate medical training. The value of radiotherapy needs re-emphasis in the medical curriculum.

With better understanding of the place of radiation, better teamwork between radiologists and those dealing with the surgical or medical management of cancer, and better analysis of accumulated clinical facts, progress in the radiotherapy of cancer should continue.

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DRUGS, DOCTORS AND DIRECTIVES*

ALBERT H. HOLLAND, JR., M.D.†

Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D. C.

The therapeutic successes of modern-day medicine are directly related to 3 factors: 1) the education and training of physicians, 2) the conduct of research, and 3) the availability of good drugs. It is apparent that each of these elements is, in turn, interrelated to the others. Although the history of medicine does illuminate and reveal the major milestones, it nevertheless does not lend strong support to a determination or conclusion as to which of these 3 factors primarily accounts for our present modest degree of therapeutic success. Perhaps it is unnecessary to deliberate the dilemma of the chicken or the egg. It is, indeed, fortunate that we have both. Likewise, it is fortunate that we have a sizable group of well educated physicians; that research is now an intensive and serious business; that many effective potent drugs are generally available; and that new and better ones are constantly being developed. Precisely because this is the situation, we are confronted with a variety of important professional problems which merit further study and attention.

Perhaps the physicians' most precious professional possession is his licensed prerogative to do whatever he considers necessary in the best interest of his patient. This is his responsibility. We physicians, as a group, have not exercised the zealous custody of these privileges which they or the public health command.

Medical Licensure

Medical licensure is a state function and is not controlled by federal statute. Unfortunately, however, state boards of medical licensure often lack the authority or effective means of coping with the mispractice and the malpractice of medicine. In consequence, there are a number of states in which small, but politically powerful pressure groups, have been able to establish for themselves legal privileges to engage in the healing arts. This, despite the fact that there is a notable absence of both healing and art. In addition, there are those unnumbered thousands engaged in all manner and means of illegal practice of the healing arts. The quacks, the charlatans, the food faddists, and the doting demons of deceptive devices cleverly appear to the unsuspecting, as tradesmen in tranquility. Yet in reality they are purveyors of pomp and privation, pain and poverty, postponement and post mortems. Tradesmen in tranquility? In truth they are tradesmen in treachery.

* Presented by William H. Kessenich, M.D., Deputy Medical Director, Bureau of Medicine, FDA, for Dr. Holland at the Annual Meeting of the American Therapeutic Society, San Francisco, California, June 19–22, 1958.

† Medical Director.

It seems clear that the doctor of medicine must assume a more aggressive role, individually and through organized medicine, if he is to protect adequately his own professional prerogatives and fullfil his professional responsibilities as a citizen of his own state.

Since most physicians are properly preoccupied with the care and treatment of their patients, it is understandable that they have been loath to divert their time and energies to this seemingly legal problem. Present-day events now make it clear that physicians can no longer afford to ignore or to leave to others the problems of legal licensure and illegal practice. Never before has medical quackery, in all forms and at all levels, been more rampant or more lucrative than now. Literally millions and millions of dollars each year are wasted on unorthodox and unproven treatment, not to mention the tragic price in human suffering and death.

The Federal Food, Drug, and Cosmetic Act

The law we administer (the Federal Food, Drug, and Cosmetic Act) requires, among other things, that a drug which moves from one state to another have the purity and strength claimed for it, and that it be labeled truthfully and properly. Thus we are able to help fight the medical quackery that depends primarily upon mislabeled drugs, and upon interstate commerce. However, the bulk of medical quackery is not subject in any manner to the provisions of the Pure Food and Drug Law. This is where the medical profession must become more active, both in its own self-interest and for its patients.

The State of California, whose hospitality we now enjoy for this meeting, has probably been the most active in considering this complex medico-legal problem. Its efforts for some years have been directed at the scourge of cancer quackery. Legislation is now pending on this subject, which should be followed carefully by medical leaders in the other 48 states. The American Cancer Society, through its Committee on Unorthodox and Unproven Remedies, has likewise devoted much time and effort to the study of this problem. It now has an abundance of information which will prove extremely helpful to state medical organizations wishing to pursue this matter aggressively.

During the last two years we in the Food and Drug Administration have had to face the unpleasant task of prosecuting licensed physicians for indulging in the illegal sale of drugs. It has always been, and still is the doctor's prerogative to dispense drugs directly to his patients for therapeutic purposes. This is not the question at issue. Regrettably, a few doctors have resorted to the large-scale sale of prescription-legend drugs (usually the barbiturates or amphetamines) in the absence of any bona fide doctor-patient relationship. The Federal courts to date have returned convictions in several cases that have been litigated. For example, a physician in Kansas City sold 18,000 secobarbital capsules within three months in addition to other drugs. Almost any taxi driver in town would take you to his place of business. There was never any element of the practice of medicine; in fact, the doctor did not even ask your name—only what color capsules you wanted (red or yellow) and how many? Twelve for a dollar. He

would sell you 12 or 100 or more; it made no difference just so long as you had the money. This man also seemed to have the local market cornered in supplying the bars, night clubs and call girls.

In Dumas, Texas, another physician was convicted for the large-scale illegal sale of stimulant drugs to Federal agents, whom he supposed to be truck drivers. The initial sale was 1,000 5-mg. amphetamine tablets. Twelve days later he sold 1,000 10-mg. tablets to the same agent, and one day after that 1,000 5-mg. tablets to a second agent in the presence of the first. Clearly this is not the practice of medicine. The conviction in the Federal District Court was appealed. The United States Court of Appeals for the Fifth Circuit affirmed the judgment. The decision stated in part: "Dr. Brown had not prepared or given them any prescription and had not physically examined either of them and had not questioned them or 'prescribed' a dosage or otherwise attempted to acquaint himself with either the physical condition or needs of either man."

Just two weeks ago another physician practicing in a small northeast Georgia town, was convicted of violating the Federal Food, Drug, and Cosmetic Act and sentenced to three years in Federal prison.

He had been a highly regarded physician in his community until he embarked upon the wholesale selling of amphetamine sulfate tablets. He specialized in selling these tablets to truck drivers for distribution to truck stops, with the ultimate consumers being truck drivers.

Acting upon complaints, a Food and Drug inspector visited this doctor and on his initial visit was able to purchase 20,000 10-mg. amphetamine sulfate tablets for the sum of $200. Approximately one week later the same inspector, still posing as a truck driver, purchased another 20,000 tablets and 1,000 half-grain phenobarbital tablets. It took the jury only fifteen minutes to return a verdict of guilty.

Let me make it abundantly clear, the Federal Food, Drugs, and Cosmetic Act does not control the practices of medicine, nor does the Food and Drug Administration have any desire to attempt to do so. When an individual engages in the illegal sale of prescription drugs, however, he is subject to all the provisions of the law, be he physician, pharmacist or layman. The barbiturates and the amphetamines are good drugs and are important and valuable tools to the physician. When sold in bulk for non-medical, antisocial, or immoral purposes, the sale is illegal and the seller is in violation of Federal law. To dispense medication for the benefit of a patient is one thing; to peddle pills is quite another.

New Drugs

Perhaps of greatest interest to the American Therapeutic Society are the activities of the Food and Drug Administration in the area of new drugs. The law defines a new drug as:

1) "Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof."

2) "Any drug the composition of which is such that such drug, as a result of investigation to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

We are now processing from 500 to 600 new drug applications annually. No doubt most, if not all of you have been called upon by the drug companies to conduct clinical investigation and evaluation of these drugs during their developmental stages. To serve as a clinical investigator is no mean responsibility, for the results of your studies must be submitted by the company to the Food and Drug Administration. This submission takes the form of a new-drug application which must contain full reports of all studies (both animal and human) conducted with the drug, as well as a complete description of the production, processing and packaging employed in the manufacture of the drug. Of equal importance is the submission of all labels and labeling proposed for use with the drug. All of these data, and more, must be reviewed and accepted by the staff of our New Drug Branch before the drug can be legally marketed in interstate commerce. This new drug procedure was enacted by the Congress as a measure for protection of the consumer. It is apparent that it also affords considerable protection and security to the physician. In essence, it means that he can rely on the safety of the drug when used as directed, with appropriate attention to the cautions and contraindications as stated in the labeling. Each important new drug must have an official brochure as part of its labeling which is a summarization of all of the pertinent information known about its use. This information is based on the work and experience as reported to the firm by the clinical investigators. You assume, therefore, the responsibility of furnishing the basis for the information which will be distributed to the medical profession at large, telling them how to use the drug effectively and safely. The clinical investigator does much more than just pursue his own intellectual curiosity or revel in the blessings of academic freedom. His, indeed, is a vital role in the business of drug development.

It would be hard to over-emphasize the importance of official drug brochures. In recent times they have even been the basis for large malpractice suit awards. Most attorneys are now aware of the availability and significance of these documents and if they can prove in court that the physician failed to read or to follow the information contained therein, they often have the makings of a pretty good malpractice case. The time has long since passed when physicians can afford to ignore the official brochures for new drugs. The dosage directions, route of administration, frequency of use, signs of toxicity, side-effects and contradications all compose the fundamental data which the doctor must know and understand if he is to employ the drug intelligently and safely. This does not mean, however, that the physician cannot deviate from the directions for use given with the drug. On the contrary, not to do so when indicated would be poor medicine and equally culpable. It does imply that the doctor must give careful consideration to the experience of his colleagues as reflected by the information in the official brochure and then proceed to accumulate and extend his own

experience with the drug. Neither the drug firm nor the Food and Drug Administration attempts to dictate how you should practice medicine or what is best for any one patient. The whole purpose of labeling information is to acquaint the physician with the known facts about a drug and its use as of a given time. It is for these reasons that it is incumbent on the physician to take the time to read the official brochure on a product. It is required of the drug firm by the Food and Drug Administration and is designed primarily for the doctor's use.

The Federal Register

Communication with and to the medical profession is a problem of ever increasing importance and complexity. The Food and Drug Administration, as all other Government agencies, is required to publish all of its official proposals and regulations in a Government publication, the Federal Register. This is the vehicle whereby we must give appropriate and official notice to the public at large of all such actions or proposed actions and regulations. Food and Drug Administration reprints of many drug notices are available to you as a free mailing-list service. Many such entries relate to drugs, their labeling and their use. Yet, I often wonder how many doctors are even acquainted with the Federal Register, let alone read it. I'm not suggesting that you attempt to read this document regularly, because it is really quite dull. It would be well, however, to consider having a Federal Register column in some of the leading medical journals, where pertinent statements could be reproduced or abstracted for your information.

CONCLUSIONS

The medical profession, and particularly organizations and societies such as yours, must devote more, and more serious, attention to the affairs of Government if they are to exert their proper share of guidance and influence.

Government must serve those who are governed. Whenever this fails or ceases, the result is oppression and tyranny. In the words of Lord Acton in a letter of Bishop Mandel Creighton,

> "Power tends to corrupt; absolute power corrupts absolutely."

True to the heritage of our American freedom and the traditions of medical practice we must be willing and be prepared to recognize and to solve the problems wherever Drugs, Doctors and Directives are concerned.

ALLOY STEEL WIRE AS SUTURE MATERIAL FOR OPEN ANASTOMOSES OF THE LARGE INTESTINE*

HOWARD D. TRIMPI, M.D.† AND GUY L. KRATZER, M.D.

Temple University School of Medicine, Philadelphia, Pennsylvania

The most common major complication of large-bowel resection is leakage at the site of anastomosis. This unfortunate accident has occurred less frequently since the general use of preoperative antibiotic medication in bowel preparation, better patient nutrition, and improved operative technics; nevertheless, its incidence continues to be disproportionately high.

We were recently called in consultation to a nearby hospital where a 46-year-old man two weeks previously had undergone a resection of the descending colon for carcinoma. He now presented a partial separation of the wound through which fecal material exuded. There had been adequate preoperative bowel preparation with cleansing enemas, oral neomycin and phthalylsulfathiazole. The patient was in excellent condition from the viewpoint of nutrition and electrolyte balance. At operation the free bowel segments had been found to have good blood supply. The anastomosis had been accomplished without tension, using an inner layer of catgut sutures and a second layer of interrupted silk sutures in the serosa. No extension of the carcinoma or evidence of metastases could be demonstrated. On the seventh postoperative day a wound abscess was discovered. When this was drained, fecal material poured from the site of the anastomosis. In reviewing this case and many similar ones, we have become convinced that when leakage occurs in well prepared patients undergoing operation performed with good technic, the suture material must be suspected. Catgut and silk both produce protein reactions when buried in tissues. These reactions are usually mild and transient, but in the occasional patient they may be severe locally. Healing is retarded and bacteria flourish at the suture sites, producing suppuration and breakdown of the anastomosis.

Nonabsorbable sutures are better than absorbable ones for joining resections of the large bowel, as there is much less protein reaction and wound approximation is maintained longer. Cotton, linen or silk fibers are permeable to bacteria and inflammatory cells; therefore alloy steel wire is superior. We have routinely employed alloy steel wire in anastomosing the bowel for the past two years. One of us (H.D.T.) has used it for five years. Our experience with its use in 156 consecutive patients has led us to conclude that it is much better than other materials for this purpose. In this series of 156 cases, only 2 fistulas developed and both of these were in patients in whom the bowel had been resected in the presence of active ulcerative colitis. There were no cases of peritonitis, and no deaths attributable to anastomotic dehiscence or leakage.

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† Address: Allentown, Pa.

EXPERIMENTAL

Methods

Prior to utilizing wire for bowel anastomoses, a study was undertaken in unselected mongrel dogs to compare the reactions toward wire, silk and catgut in unprepared intestine. Twenty-one animals were subjected to resections of the colon. In each, 3 anastomoses were performed at locations about an inch apart; each anastomosis followed complete division of the bowel. Each closure was made using one layer of interrupted through-and-through sutures of the selected material, with knots tied on the inside to invert the bowel. To insure as much experimental control as possible for the 3 different suture materials in each dog, the same number of sutures was used in each closure. The positions of the 3 materials were varied from animal to animal so that the position of the different closures would be equally divided among the anastomoses.

Results

In 12 of the 21 dogs, leakage occurred and resulted in peritonitis. These dogs were immediately sacrificed and the segment of colon containing the anastomoses was removed for microscopic sectioning.

Inspection revealed leakage at the catgut closure in 7 and at the silk closure in 5. There were no perforations and no evidence of leakage at the wire closures. Perforations at the site of the catgut sutures resulted in earlier postoperative mortality than did perforations at the site of the silk sutures (Figs. 1, 2 and 3).

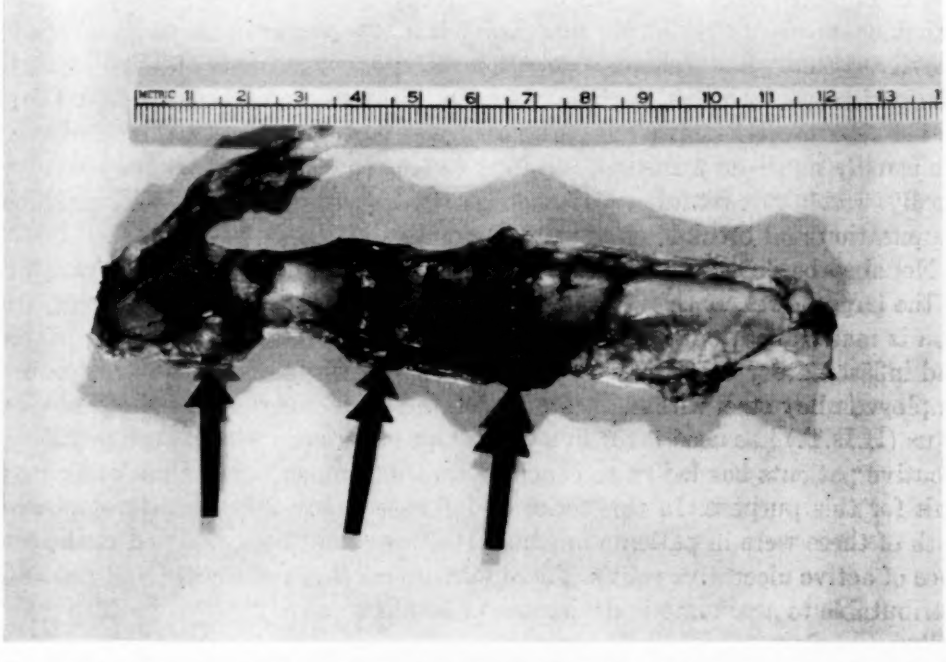

FIG. 1. Specimen containing 3 anastomoses. Perforation of catgut suture line (right arrow) caused peritonitis on the fourth postoperative day. Wire suture line is in the center, and silk to the left.

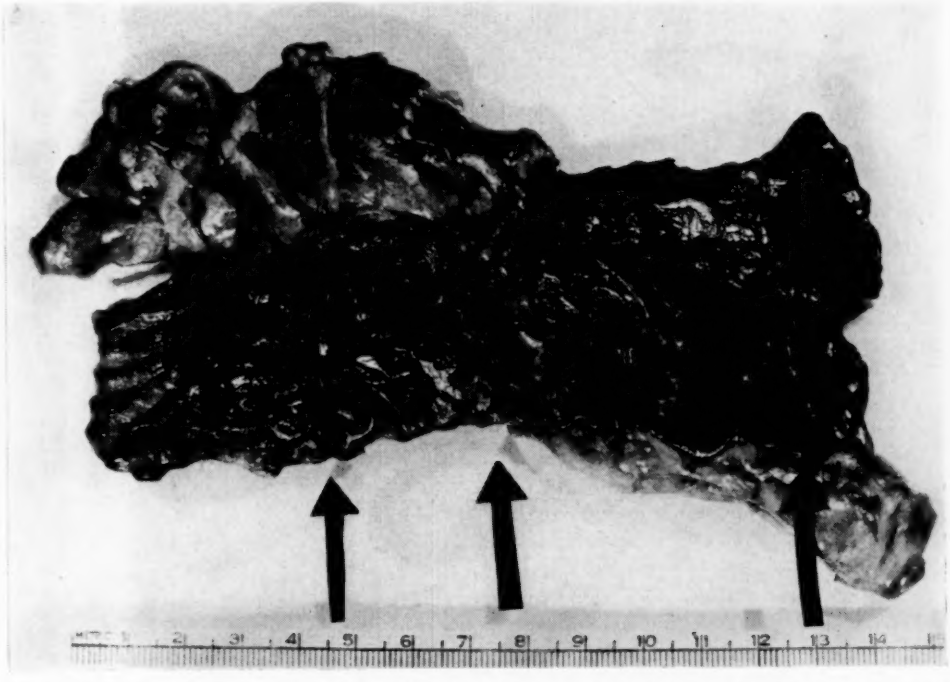

FIG. 2. Perforation at silk suture line to left caused fistula on twelfth postoperative day. Note smooth wire closure to the right. Some fragments of chromic catgut remain at the center anastomosis.

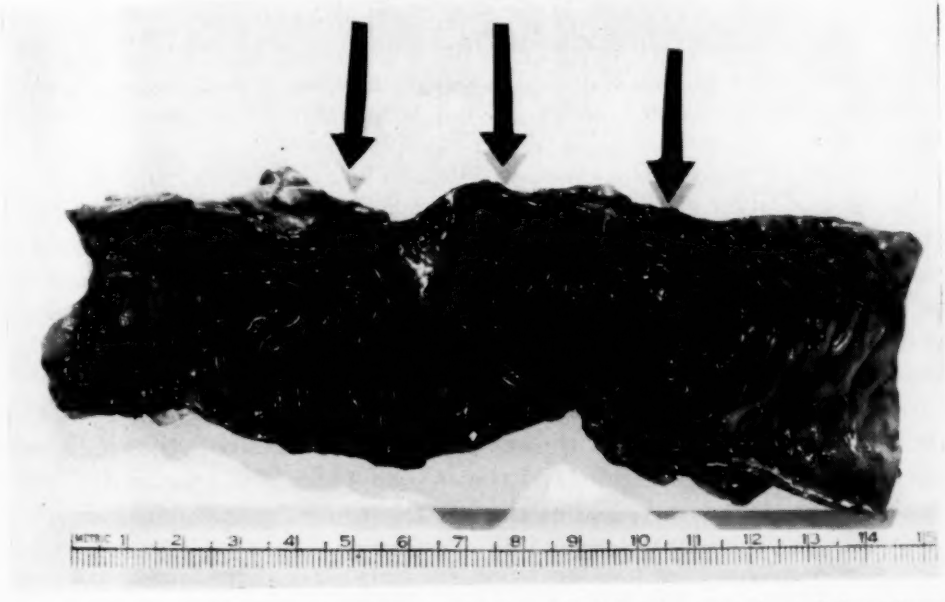

FIG. 3. There is leakage at the right suture line (silk) due to necrosis and sinus formation. The catgut suture line is in the center. The wire closure is at the left. Specimen removed on tenth postoperative day.

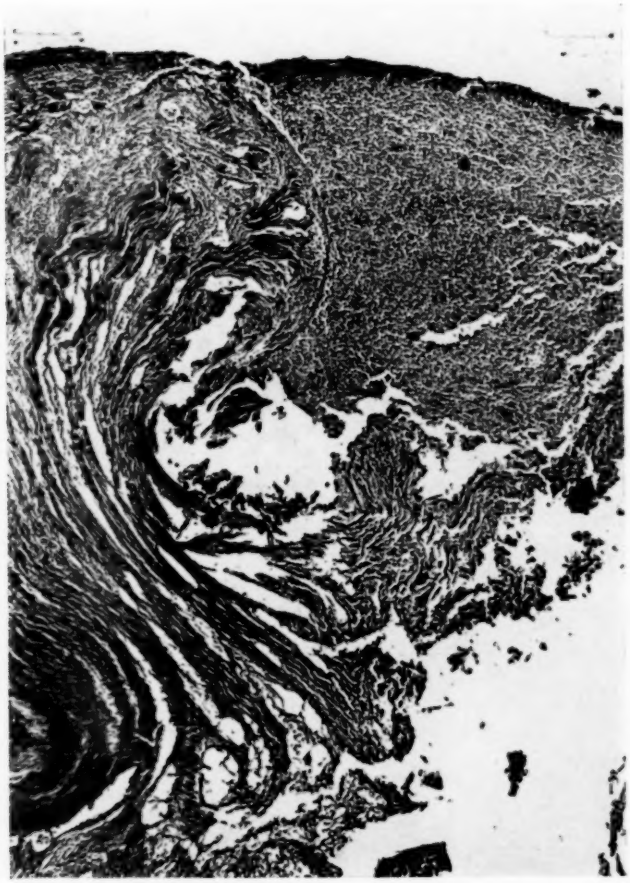

FIG. 4. Microscopic section of a chromic catgut suture line reveals leukocytic infiltration with suppuration and destruction of suture fibers. Specimen obtained on fifth postoperative day.

Microscopic study of the catgut suture areas revealed much involvement by bacteria, leukocytes and inflammatory cells, with suppuration (Fig. 4). At the site of the silk closure there was inflammatory reaction with bacteria, suppuration and sinus formation leading from the lumen of the bowel out to the serosa along the silk strands (Fig. 5). At the site of the wire closures there was only pressure necrosis in a few instances, with minimal inflammatory reaction (Fig. 6).

In 9 dogs surviving six weeks, the segments of colon containing the anastomoses were removed and studied. Figure 7 shows such a specimen; the central suture is wire, at the right is silk, and at the left is catgut. Transillumination reveals the characteristic induration found at all closures (Fig. 8). There was a large amount of inflammatory infiltration at the catgut and silk suture lines. The induration found at the site of wire closure appeared to be due to a tendency on the part of the operator to tie the sutures too tightly, thus constricting the tissue. Microscopic examination of the six-week specimens revealed inflamma-

FIG. 5. Microscopic section of silk suture line on twelfth postoperative day reveals inflammatory reaction and infiltration of silk fibers by leukocytes and bacteria. Sinus formation is taking place.

tory reaction at all closures. The most severe inflammation was at the silk suture lines, where sinus formation and excess granulation tissue was often noted. At the catgut lines the inflammation appeared to be resolving, although small particles of unabsorbed catgut were numerous.

CLINICAL

Alloy steel wire was used in 156 cases of large-bowel resection. In 87 patients the operation was a colon-rectum anastomosis in which a single layer of interrupted braided alloy steel wire was employed in a well-prepared bowel; no perforations developed. Among 18 transverse colostomies repaired by open end-to-end anastomosis, there were no perforations. Multiple colotomy wounds were repaired in 37 instances. Among 14 patients who underwent other types of colon resection, there were no complications at the site of anastomosis. In 2 patients in whom the ileum had been anastomosed to the rectum following colectomy for ulcerative colitis, perforations occurred which resulted in pelvic abscesses and fistulae.

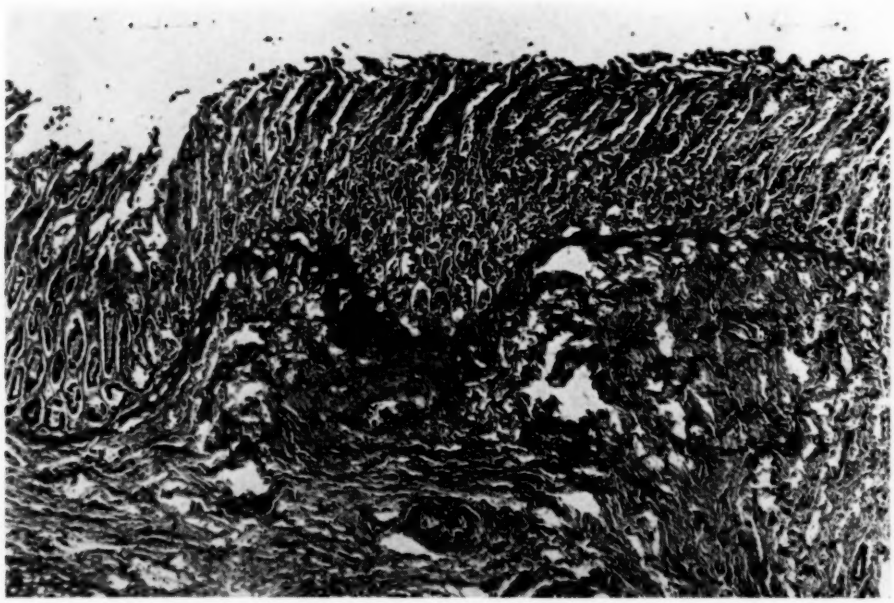

FIG. 6. Microscopic section showing a wire suture line after six weeks. Note excellent healing. (Wire suture removed before sectioning tissue.)

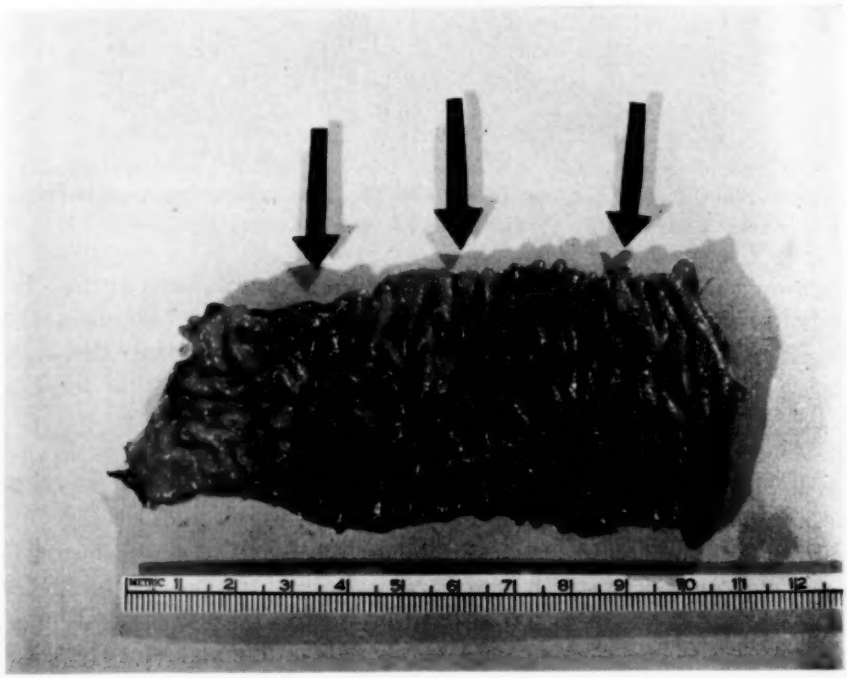

FIG. 7. Specimen removed six weeks after operation. Silk suture line is to the right. Wire suture line is in the center. Chromic catgut closure is to the left. The same specimen is transilluminated in Figure 8.

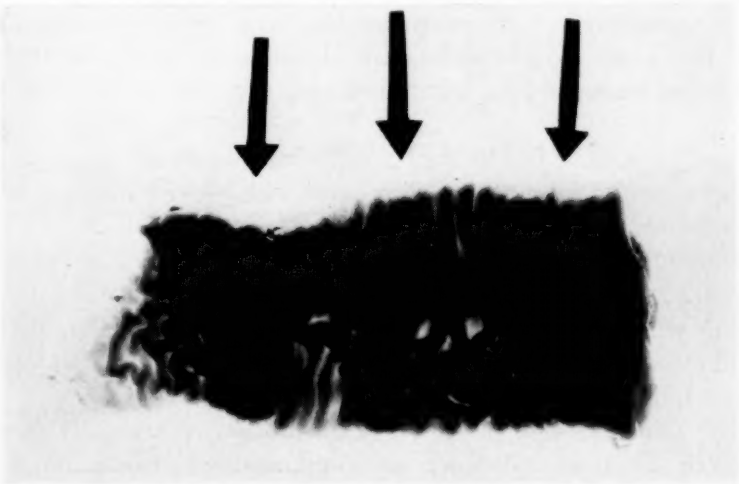

FIG. 8. Transillumination of specimen shown in Figure 7. Note marked induration surrounding silk suture to the right, moderate induration around chromic catgut to the left (subsiding after six weeks), and minimal involvement around wire suture in the center.

Thus, among the 156 patients in whom alloy steel wire had been employed for open end-to-end anastomosis, there were 2 perforations at the suture lines, an incidence of 1.3 per cent.

DISCUSSION

Babcock (1) was the first to advocate the use of alloy steel wire as suture material. His studies, classic in demonstrating the safety of this suture in the presence of infection, indicated that wire was of particular value in repairing hernias, abdominal wound fistulae, and defects in the bile duct, pancreas and intestine. Experimental and clinical studies conducted by Pratt (2), Preston (3) and Large (4) confirmed the advantages of buried wire. Holland (5) found it excellent for esophageal anastomoses. The present study focuses attention on the value of alloy steel wire in anastomoses of the colon.

Chromic catgut degenerates rapidly in an infected field. It produces a local foreign-protein reaction that delays healing. Silk causes less foreign-protein reaction than catgut, but when it is used as a single-layer through-and-through suture, it tends to promote sinus formation through the bowel wall due to bacteria becoming enmeshed in its fibers. Granulations frequently surround silk material exposed in the bowel lumen.

In the human colon, simple through-and-through one-layer closures are the best, because the immediate blood supply at the open bowel edge is not impaired, and the intestinal lumen is not narrowed. We have found braided number five "O" alloy steel wire to be the most satisfactory for such sutures. There is no foreign-protein reaction and the suture is not permeable to bacteria. Sinuses do not develop nor is there granulation formation in the bowel wall or lumen.

Particularly successful in our experience has been the anastomosis of colon to rectum by the single-layer through-and-through braided wire method when there is no rectal serosa to lend additional support.

CONCLUSIONS

In the experimental laboratory, alloy steel wire proved superior to catgut or silk for anastomosing the colon in mongrel dogs.

In the human colon, the incidence of perforation at suture lines was much reduced when braided alloy steel wire was employed. In only 2 patients among 156 in whom wire sutures were employed did fistulae develop; both of these patients had ulcerative colitis at the time the attempt was made to join the ileum to the rectum following colectomy.

Alloy steel wire does not cause a foreign-protein reaction. It is superior to cotton, linen or silk, in that its fibers are impermeable to bacteria and inflammatory cells. Sinuses and suppuration rarely occur.

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ARTERIOSCLEROSIS OBLITERANS; AN EPITOME*

BERT SELIGMAN, M.D.†

Surgical Service, Flower Hospital, Toledo, Ohio

Arteriosclerosis obliterans is a degenerative occlusive arterial disease which occurs seven times more frequently in the male than in the female and is complicated by diabetes in about 40 per cent of cases and by hypertension in 20 per cent. It is a disease which affects the large and medium-sized arteries. Although it may occur at any age, it usually manifests itself in patients around the age of 50. Pathologically the lesion in arteriosclerosis obliterans is characterized by destructive degeneration or thinning of the tunica media, atheroma formation, and thrombosis. Since the time of Virchow, when he elaborated the cholesterol theory in the etiology of this disease, not much has been added to our knowledge of it. Virchow stated that fat-laden phagocytic cells or lipoproteins were enmeshed in the interstices of the tunica intima following mechanical irritation, and that after a suitable number had been so trapped, calcification took place with the formation of the atheroma. Rokitansky, who was a contemporary of Virchow, advanced a theory which even today has some adherents. He felt that a thrombus was the nidus for the formation of an atheromatous plaque and that the plaque was a result of cholesterol invading the thrombus with subsequent calcification. We still do not know exactly how the process begins and experimentation has not offered much in the way of solution of the problem. The rabbit (1) has been used in many experimental laboratories, but this is not exactly a wise choice because: 1) the amount of cholesterol which must be fed to a rabbit is astronomically high; 2) due to the huge amounts of cholesterol which are fed, not only do the coronary and peripheral vessels become the sites of atheroma, but even the parenchymatous organs are involved; 3) cholesterol is foreign to the natural diet of the rabbit, and 4) sad to relate, there is no similarity between the lesion experimentally produced in the rabbit and that which occurs naturally in man.

Gofman's serum S_f 12–20 lipoproteins (2), which he distinguished with the use of the ultracentrifuge in 1950, were reported to be useful as a predictive agent in screening out potential sufferers of coronary or peripheral arteriosclerosis. After much work and a cooperative study conducted by the National Heart Council (3), all that could be said of the S_f 12–20 lipoprotein test was that it was an expensive and complicated method of determining the serum cholesterol level. The exact role of cholesterol is still to be ascertained. The cholesterol which seems to be involved in the process of arteriosclerosis obliterans is an endogenous compound which can be synthesized from water and acetate and is not to be confused with the exogenous cholesterol which is the result of our diet. Thus 2 patients may each have a blood cholesterol level of 300 mg. per 100 cc., yet one may be

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† Chief of Service, Vascular Surgery.

free of any signs or symptoms of arteriosclerosis obliterans whereas the other presents clinical evidence of the disease. This is an over-simplification of the serious problem involved, but it is evidence that heredity cannot be discounted as one of the important factors in this disease. If the parents and their ancestors did not have coronary or peripheral arteriosclerosis, the possibility is that the offspring will not have it.

SYMPTOMS AND SIGNS

The symptoms of the disease are intermittent claudication, cold, tight-skinned and wet feet, numbness, tingling, burning paresthesia, and pain at rest. Claudication means lameness, but the term has been prostituted so that now it has other connotations. Such symptoms as aching, pain and muscular cramps are all described as claudication. Rest pain is just that; it is pain that occurs in an extremity when the patient either sits or lies down. It is probably due to the decrease in muscular activity or to the gravitational effects of being in the supine position, as these factors can cut off the additional thin trickle of blood which is so necessary to maintain the viability of the extremity, whereas in the upright position, the reduced flow of blood is augmented by exercise. Since the lumina of the arteries are less patent because of disease than are the lumina of the veins, the blood drains out very quickly, ischemia is increased, and rest pain occurs. It is not to be confused with nocturnal cramps, which are involuntary muscular contractions brought on by rest and relieved by exercise, and can occur in anyone.

Cold, wet and tight-skinned feet, numbness, burning and pain are related to the degree of ischemia present. These symptoms indicate that because of deficient circulation the nerves themselves are deprived of sufficient oxygen and nourishment to maintain proper function. A distinction must be drawn regarding diabetic neuropathy, in which both sensory and autonomic nerves are involved. Diabetics may have good arterial circulation along with their neuropathy, and yet be erroneously classified as arteriosclerotics because of the presence of injury, cellulitis, or gangrene which may have been produced by such things as a hot-water bottle, a heating pad, an icebag, or injudiciously performed surgery on a toe nail, corn or callus. In a diabetic with good dorsalis pedis and posterior tibial pulses, the vessels may later become arteriosclerotic, but usually a young diabetic with early neuropathy does not have arteriosclerosis obliterans. The signs of arteriosclerosis obliterans are alterations in pulses, toe-skin temperature differences, cutaneous color changes, edema, and trophic changes in the skin.

As in any branch of medicine, in peripheral vascular disease it is essential that an adequate history be taken, a thorough physical examination be made, and certain laboratory procedures be performed to facilitate making the correct diagnosis as well as establishing the degree of disease present. It is necessary to establish the presence or absence of dorsalis pedis, posterior tibial, popliteal, femoral and aortic pulses. It is wise to remember that the dorsalis pedis pulse is absent unilaterally in 14 per cent of persons, and bilaterally in 7 per cent; even the posterior tibial pulse is absent in 2 per cent of all patients examined. After

the presence or absence of pulses has been ascertained, the type of pulse (if present) must also be noted.

Skin temperatures, if they are to be of statistical significance, must be taken under basal conditions, namely, nothing to eat or drink after midnight, arrival at the laboratory at an early hour in the morning, and measurements made at a room temperature of 60 to 65°F. or 20 to 25°C. The patient is placed on the table, stripped to the waist, and allowed to remain there for thirty to sixty minutes to become adjusted to the temperature of the room. To be statistically significant, skin temperatures also must be accurately recorded, because differences in temperature between the toes of one foot compared to the other, or differences in temperature between the various toes of one foot are of great importance. Toe-skin temperatures may vary from 24°C. to 32°C., depending upon conditions existing at the time of the study. Of significance is a difference of 1 or 2 degrees between the digits of one foot.

The reflex vasodilatation test can be utilized advantageously to predict the immediate effect of lumbar sympathectomy, as well as the long-term outlook. As to oscillometry, no information can be gained by this procedure that cannot be duplicated by a well trained sensitive examining finger. Plethysmography can be employed to measure blood flow to a part, but the results are of more significance from a statistical than from a clinical standpoint. A procedure which has assumed increasing importance, not only in facilitating diagnosis but also in permitting more definite plans for treatment, is the injection of a radiopaque dye intra-arterially. The information thus gained can be obtained by no other method. Collateral circulation is outlined, the site of the obstructive process is localized, and the proximal and distal portions of the vessel are visualized and evaluated with respect to surgical intervention.

Cutaneous color changes are important from the standpoint of assessing the severity of the disease. Pallor on elevation, rubor on dependency, and a fairly normal color in the supine position would indicate either a mild or moderate disease process. If the pallor persists for several minutes after placing the foot in the dependent position, it is an ominous portent; so also is persistent rubor upon elevating the foot. Pallor is caused by the rapid venous draining of the blood which is in the arterioles and capillaries. Rubor usually indicates a degree of ischemia which is severe. The accompanying capillary paralysis is secondary to anoxia and malnutrition and leads to increased capillary permeability with extravasation of blood and its cellular elements into the surrounding tissue.

The circumstances which give rise to rubor are also capable of producing edema due to the same alteration in capillary permeability. The edema of arteriosclerosis obliterans is usually on a dependency basis. The patient has discovered that on lying down with the feet level with the body, pain occurs in the extremities, and that by sitting up and allowing the feet to hang over the sides of the bed or by sitting in a chair with the feet down, the pain is ameliorated. Early edema can be easily cleared up, but if it is persistent it is difficult to abolish. Edema, by compressing the already compromised arteries, produces a further restriction of the blood supply, thereby perpetuating the process.

FACTORS IN PROGNOSIS

The natural history of arteriosclerosis obliterans does not follow a standard pattern. In some patients the disease once having manifested itself, continues on its inexorable course and results in incapacity, loss of limb and even life. In others, great improvement may take place under conservative medical management, or even without specific medical counsel. Just how much benefit should be attributed to medical therapy is a problem. When gradual improvement has occurred over a long period of time while the patient has been taking a vasodilating drug, evaluation is difficult, since there is no known investigative method which will delineate improvement as being spontaneous or directly attributable to the medication being used.

The most important factor in prognosis is whether the disease is proximal or distal in the extremity. When the proximal portion of the common femoral artery is involved in an arteriosclerotic process and segmental occlusion has occurred, the collateral circulation comes into play so that the obstructed segment can be by-passed. This does not represent new circulation, but rather newly utilized vessels. The higher one goes in the arterial tree the larger and more numerous will be the collaterals available for by-passing. Lower down in the arterial tree the vessels become smaller and as a consequence, when an obstruction occurs, the collateral circulation will be made up of either smaller (even tiny) or fewer vessels than would be found higher up. Thus the location of the disease, whether it be proximal or distal, is probably one of the most important points to be weighed in prognosis.

TREATMENT

Medical

Medical treatment consists of education as to care of the feet and utilization of measures designed to increase nutrition to the part by means of vasodilatation. Patients must be told that because of diminution in the blood supply to the feet, continued special care is necessary to prevent serious difficulties. The feet must be washed each night with mild soap and warm water, and the spaces between the toes are to be handled gently but thoroughly. After drying the feet carefully, vaseline or lanolin ointment is gently massaged into the skin. The feet must be kept warm at all times, using clean woolen socks changed daily during the winter, and white cotton socks in warm weather. Long heavy underwear should be worn. The feet must be protected from injury at all times, this being facilitated by wearing properly fitting shoes. Loose-fitting bed socks should be worn at night. Since the circulation is already compromised, no unnecessary demands should be made upon it by injudicious use of hot-water bottles or electric heating pads. Toe nails should be cut straight across; the cutting should be performed in a good light and after the nails have been softened by a 20-minute soak in warm water. No self-surgery on corns or calluses should be permitted. The patient should drink 3 to 4 quarts of water daily and eat liberal quantities of fresh vegetables; for diabetics, strict adherence to diet is necessary. Tobacco is prohibited, circular garters are not to be worn, and if anything unusual de-

velops (such as a blister, infection or exaggeration of symptoms) a physician should be consulted immediately. In addition to these common-sense measures an endeavor should be made to secure vasodilatation either reflexly, or by therapeutic amounts of whiskey, glycine powder, nylidrin (Arlidin), tolazoline (Priscoline), or dibenzyline. De Bakey and associates (4) have reported that when a sympatholytic drug is given by mouth or parenterally, an adverse effect may be produced. Blood flow follows the path of least resistance, so that when general vasodilatation ensues, more blood flows into the healthy than into the diseased arteries, thereby reducing further an already impaired blood supply. Learmonth (5) has stated that there is not as yet a suitable sympatholytic agent, and decries the intra-arterial injection of these drugs.

Surgical

The surgical approach to the treatment of arteriosclerosis obliterans encompasses lumbar sympathectomy, thromboendarterectomy, and blood vessel grafting. Sympathectomy is of value in patients who are not candidates for thromboendarterectomy or for grafting. Patients who have intermittent claudication, cyanosis, increased sweating, and signs of peripheral vasoconstriction lend themselves to sympathectomy—which should be complete. Since 1953 the operation has been modified so that the twelfth thoracic and the first, second and third lumbar ganglia are extirpated through an incision which in some instances involves partial resection of the twelfth rib. According to Slessor's (6) recommendation, if the ganglia cannot be identified, then a 10-centimeter portion of the chain is removed. Patients should be carefully selected for sympathectomy, because improper selection will cause a good operation to fall into disrepute. For example, in each of 2 patients, claudication of the calf may develop on walking and all pulses may be present; after walking the distance necessary to produce claudication, the pulses may still be present in one patient but absent in the other. In the former, the presence of pulses after walking indicates that the vessels which supply the calf muscles are thrombosed and thus a sympathectomy would be of no value. In the latter, the fact that the pulses disappeared with exercise would seem to indicate that the blood supply of the calf muscles was reduced by spasm in the large vessels and that sympathectomy would be beneficial.

Due to the possibility of re-thrombosis, rupture of the suture line, or the possibility of aneurysmal dilatation, thromboendarterectomy is not the procedure of choice in most cases. It may be used to clear the proximal or distal portions of the host artery preparatory to grafting, but other than this, the indications for its use are limited.

After much trial and error and many false starts, blood-vessel grafting has finally come of age. Arterial continuity can be restored with autogenous venous grafts, homologous arterial grafts, or synthetic fabric grafts fashioned from nylon, orlon, vinyon-N or dacron. In grafting procedures it is mandatory not only that there be a good proximal outflow into the graft but that the distal portion of the host artery be adequate to provide an outflow capable of handling the

volume of blood conveyed to it. As to the comparative merits of plastic prostheses versus homografts, each has its proponents. In both experimental animals and human subjects, homografts can be the site of the same atherosclerotic process that has developed in the host vessels. This indicates that as systemic arteriosclerosis grows worse, it will eventually involve the graft. Plastic prostheses, on the other hand, do not become similarly involved. The ease of insertion of the homograft and the manner in which it can be manipulated at the time of placement make it a more ideal type of graft for the surgeon. Efforts are being expended by many people interested in the problem of grafting for the development of the so-called perfect plastic vessel graft.

SUMMARY

Arteriosclerosis obliterans is a degenerative occlusive arterial disease.

The etiology is still controversial, some of the difficulty being due to the various interpretations placed on the experimental and clinical findings.

The pathologic physiology is related to ischemia produced by obstruction, either partial or complete, of the vessel involved.

Treatment may be medical or surgical; both methods are necessary in selected cases.

Restoration of continuity of blood flow by means of vessel grafting seems to offer the most promise to afflicted patients at this time.

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A METHOD FOR THE STUDY OF PERIPHERAL ARTERIOSCLEROSIS* †

TRAVIS WINSOR, M.D., E. K. FISHER AND J. HOWARD PAYNE, M.D.

The Departments of Medicine and Surgery, University of Southern California, Los Angeles, and the Heart Research Foundation and the Foundation for Surgical Research, Los Angeles, California

The purpose of this report is to describe a method for the study of the peripheral circulation which is useful for showing changes in the blood vessels due to arteriosclerosis. The method may be used to evaluate objectively the results of surgical or medical treatment and is applicable to the study of arteriosclerosis. The technique is suitable for studies in man or in large animals such as dogs. It is performed quickly and may be repeated at intervals without harm or discomfort. The method measures physical characteristics of the arteries which may be correlated to advantage with the blood levels of cholesterol, phospholipids or other elements possibly related to arteriosclerosis.

METHODS AND MATERIALS

The method has been employed in more than 2000 patients with arteriosclerosis of the peripheral blood vessels of the lower extremities. Examinations were made on more than 100 patients before and after corrective surgery of the large vessels (arterial homografts); of these, 10 were selected as subjects for illustration in this paper. The examination was conducted after five to ten minutes of rest in a comfortable room. The instrument employed was a multichannel plethysmograph (Vasograph®)[1] (1).

Method. A cuff was applied to a wrist and to an ankle, and volume changes (pulsations) were recorded on a two-channel recorder. The pulse volume was compared with a standardization so that the pulse from the patient could be read in terms of milliliters of volume change per pulse beat. In order to select the proper pressure in the cuff, the following procedure was carried out. The systolic and diastolic pressures at the brachium were determined by the conventional auscultatory technique. The cuffs were inflated simultaneously to about systolic pressure, and a short record was made and standardized. The pressure in the cuff was then decreased by 10 mm. Hg, and again a short record was made and standardized. The procedure was repeated until records had been made at cuff pressures which were 10 to 20 mm. Hg below the diastolic pressure. Examination of the records showed that normally, in curves made during periods of high cuff pressure (above diastolic), a wide angle of almost 90 degrees was formed at the junction of the last portion of the catacrotic limb of one pulse wave with the first portion of the anacrotic limb of the following wave. At diastolic pressure this angle became more acute. The low-pressure curves (below diastolic pressure) had configurations which were similar in form to the acute-angle curves which occurred at diastolic pressure, but their amplitudes were lower. The pressures at which the tallest curves occurred were noted. After the pressures had been selected they were delivered to each cuff and simultaneous pulsations from the upper and lower extremities were re-

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We are grateful to Sally Cody and Mary Ann MacIntyre for their technical assistance.

[1] Electro-Medical Engineering Co., Burbank, Cailfornia.

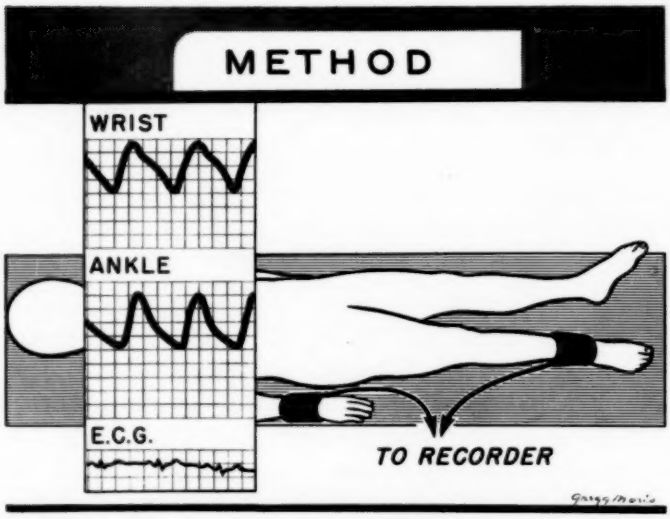

FIG. 1. Simultaneous pulse waves are recorded from an ankle and a wrist. The electrocardiogram can be used for timing purposes but is not required in the calculation of the ankle/wrist ratio.

corded (Fig. 1). The ratio of the amplitude of the pulsations of the ankle to those of the wrist (ankle/wrist ratio) was then determined. This ratio tends to eliminate the cardiac effects on the peripheral circulation, as the cardiac output is common to the wrist and to the ankle.

The technique as applied to arteriosclerosis assumes that arteriosclerosis of the peripheral vessels rarely involves the vessels of the arms and commonly involves the aorta and the vessels of the lower extremities. The normality of the vessels of the arms can be established by the absence of symptoms, the equal blood pressure bilaterally, the normal contour and amplitude of the pulse curves, and the normal appearance of the upper extremities on physical examination.

Blood cholesterol levels were determined by a modification of the Bloor technique (2). Lipid phosphorus determinations were made by a modified Youngburg method (3). Phospholipids were calculated by multiplying the lipid phosphorus value by 25. A cholesterol/phospholipid ratio was calculated by dividing the cholesterol value by the phospholipid value.

All patients were ambulatory and had been taking a low-cholesterol, low-fat diet for three or more months prior to these studies.

RESULTS

Effect of graft at the bifurcation of the aorta on ankle/wrist ratio

A 49-year-old man with arteriosclerosis obliterans involving the abdominal aorta and the iliac arteries was examined before and after an arterial homograft at the bifurcation of the aorta (Fig. 2). There was no significant difference in the pulse curves from the wrist before and after surgery. The ankle curves, however, showed a definite increase in amplitude after surgery as compared with the preoperative curves. The ankle/wrist ratio was 0.3 before operation and 1.0 after operation, which represented a threefold increase in the ratio as a result of the surgical procedure. Other changes occurred also. Following operation, the time

interval between the trough of the wrist curve and the trough of the ankle curve was decreased, and the crest time became shorter. The pulse waves were not of normal form, however, as the dicrotic notch was absent after the surgery. The finding that the height of the wrist pulse did not change but the height of the

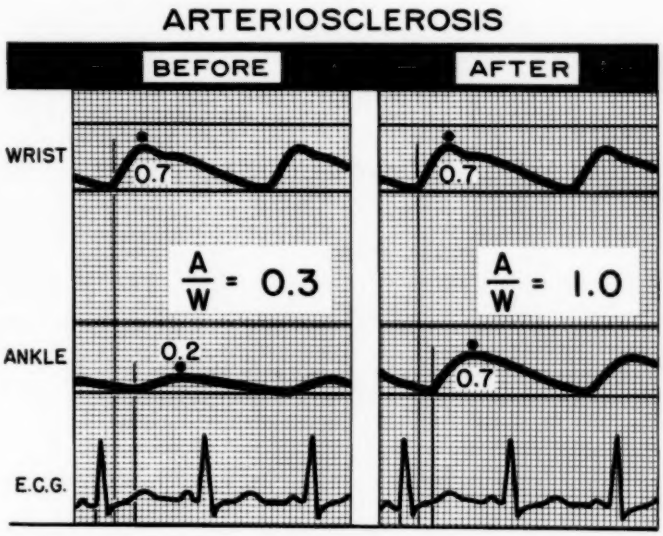

FIG. 2. The ratio of the height of the ankle curve to the height of the wrist curve increased significantly in a man with peripheral arteriosclerosis as a result of a homograft at the aortic bifurcation. This suggests improved circulation of the lower extremities. Before surgery the patient could walk half a block without leg pain; after surgery he walked for ten blocks at the same rate of speed and still did not have leg pain.

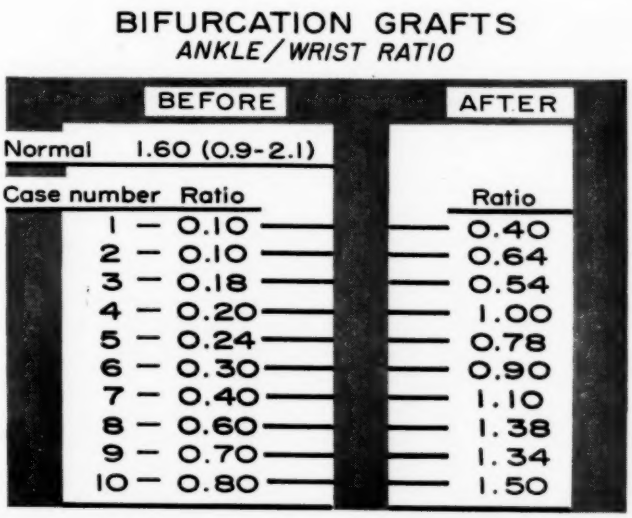

FIG. 3. Ankle/wrist pulsation ratios in 10 patients with arteriosclerosis obliterans. The records were made before and after insertion of homografts at the aortic bifurcation. In all there was a significant increase in the ratio, which was correlated with improvement in their clinical condition.

ankle pulse increased after operation suggested that the peripheral circulation to the lower extremities had been improved.

Effect of grafts at the bifurcation of the aorta (10 patients)

All the patients had arteriosclerosis of the abdominal aorta and iliac arteries and were studied before and after arterial homografts. Preoperatively all of them

TABLE 1

Effect of levo-triiodothyronine and triiodothyroacetic acid on the levels of blood cholesterol and lipid phosphorus (mg./100 ml.) and on the cholesterol/phospholipid ratio. (B = Before, A = After.)

	L-Triiodothyronine		Triiodothyroacetic Acid	
	B	A	B	A
Chol.	319.5 (230–447)	262.9 (222–320)	301 (230–406)	246 (196–341)
Phos.	15.75 (11.4–26.4)	11.0 (7.0–15.1)	14.1 (19.4–8.2)	10.7 (4.0–18.4)
C/P	0.85 (0.67–1.23)	0.998 (0.68–1.25)	0.89 (0.67–1.15)	1.01 (0.52–2.06)

TABLE 2

Effect of beta pyridyl carbinol and SC 8246 on blood cholesterol and phosphorus levels (mg./100 ml.). (B = Before, A = After.)

	Beta Pyridyl Carbinol		SC 8246	
	B	A	B	A
Chol.	321 (280–375)	272 (222–330)	316 (278–366)	259 (246–330)
Phos.	14.08 (8.2–20.4)	12.4 (9.9–16.7)	14.5 (12.0–20.4)	14.2 (11.4–20.4)
C/P	0.96 (0.72–1.47)	0.889 (0.73–1.04)	0.87 (0.72–1.05)	0.77 (0.49–1.09)

TABLE 3

The effect of safflower oil and corn oil on blood levels of cholesterol and lipid phosphorus (mg./100 ml.) and on the cholesterol/phospholipid ratio. (B = Before, A = After.)

	Safflower Oil		Corn Oil	
	B	A	B	A
Chol.	343 (280–428)	295.5 (242–380)	321 (254–447)	286 (209–420)
Phos.	14.39 (10.8–18.4)	12.39 (8.7–19.4)	12.6 (8.2–18.4)	11.8 (7.0–17.2)
C/P	0.98 (0.84–1.07)	0.98 (0.73–1.21)	1.04 (0.88–1.24)	0.98 (0.89–1.20)

had intermittent claudication after walking one to two blocks. After surgery the ankle/wrist ratio was improved significantly in all patients (Fig. 3), and the walking distance was improved to such a degree that in many cases pain did not develop after the patient walked slowly for half a mile.

Repeated tests on 5 normal subjects

In each of 5 normal subjects between the ages of 30 and 55, measurements were made daily for ten days. The ankle/wrist ratios did not show variations greater than ± 15 per cent in any subject from day to day.

Attempts to correlate blood fat levels with ankle/wrist ratios

Reduction of blood cholesterol levels: 1) Levo-triiodothyronine (Cytomel®) and triiodothyroacetic acid (triac). Ten patients were studied before, and for one month after therapy. The dosage of levo-triiodothyronine was 50 micrograms daily and that of triiodothyroacetic acid was 2 mg. daily. As shown in Table 1, a fall in blood cholesterol and lipid phosphorus concentration occurred with both drugs, and the cholesterol/phospholipid ratio was increased.

2) Beta-pyridyl carbinol (Roniacol®) and SC 8246 (16,alpha-chloroestrone 3-methyl ether). Ten patients were included in each group (Table 2). Control cholesterol and lipid phosphorus levels were determined before treatment, and one month after therapy. The dosage of beta-pyridyl carbinol was 750 mg.

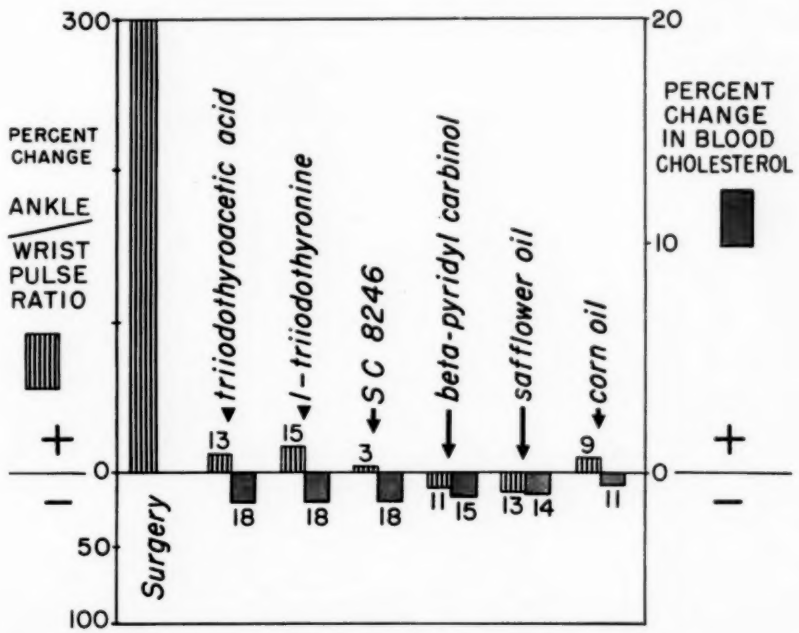

FIG. 4. Surgery produced a marked increase in ankle/wrist ratios and improved the circulation clinically, in that there was less intermittent claudication in all patients. Drug therapy lowered the blood cholesterol level but significant increases in the ankle/wrist ratios did not occur; intermittent claudication was unchanged. This may have been because the duration of drug therapy was only one month.

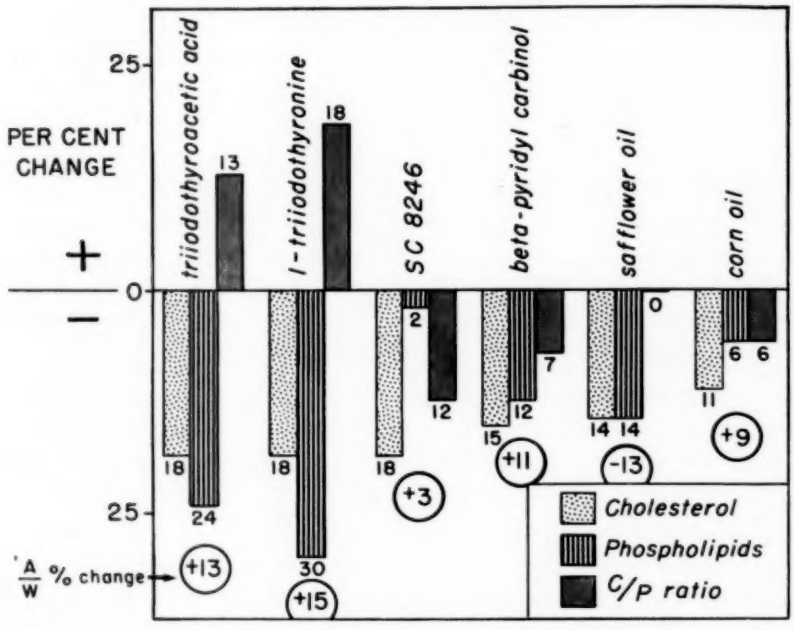

FIG. 5. The percentage change in blood cholesterol and lipid phosphorus levels and in cholesterol/phospholipid ratios (derived from Tables 1, 2 and 3). Although there was a fall in the cholesterol and lipid phosphorus levels and a variable effect on the cholesterol/phospholipid ratio, the ankle/wrist ratio did not show any evidence of increased circulation to the limbs. This may have been because the period of observation was short.

daily and that of SC 8246 was 15 mg. daily. With both agents the average blood cholesterol level fell but the lipid phosphorus levels changed only slightly. With beta-pyridyl carbinol the cholesterol/phospholipid ratio changed very little, but with SC 8246 there was a slight decrease.

3) Safflower oil (Saff®) and corn oil. The dosage of each was 1 ounce twice daily for one month. Each emulsion contained equivalent amounts of linoleic acid. With both agents the blood cholesterol level fell and there was a slight decrease in the lipid phosphorus level. There was either no change or only a slight change in the cholesterol/phospholipid ratio.

Blood cholesterol levels and ankle/wrist ratios. The percentage change in both the ankle/wrist ratio and the blood cholesterol level after one month's treatment with the foregoing cholesterol-reducing agents is shown in Figure 4. There was a large increase in the ratio following surgery, indicating improved circulation to the limbs; however, with the drugs employed, the ankle/wrist ratio did not fall in any instance outside the range of normal variability even though the blood cholesterol level fell as much as 18 per cent in some cases.

Ankle/wrist ratios, blood cholesterol and lipid phosphorus levels, and cholesterol/phospholipid ratios. The ankle/wrist ratios did not clearly indicate improved circulation to the limbs in any case and could not be correlated with falls in the blood cholesterol and lipid phosphorus levels or with changes in the cholesterol/phospholipid ratio (Fig. 5).

DISCUSSION

The technique described has certain advantages and disadvantages. One advantage is that the physical state of the arterial system is studied. The presence of abnormally rigid or flaccid vessels or obstructions in the vascular tree results in pronounced changes which are readily noted in the volume pulse curves. Also the technique has the advantage of being objective. It is standardized so that studies carried out by different technicians and on different instruments can be compared. The method is suitable for use in a large number of patients, as it can be carried out quickly by an experienced technician. Another advantage is that it is applicable to the study of large animals such as the dog. The main disadvantage is the necessity for the selection of the proper pressures in the cuffs for the upper and lower extremities. Errors in selection of the pressures can lead to errors in the ankle/wrist ratios. Nevertheless, we have found the method sufficiently accurate to reveal the beneficial effects of surgery on arteriosclerotic vessels.

The results of these studies show that surgical procedures (arterial homografts) on the large arteries have a profound restorative effect on the circulation to the lower extremities, whenever obstructions in the large vessels of the lower limbs are removed. After successful surgery these patients often have higher cutaneous temperatures in the toes. The blood flow of the toes increases, intermittent claudication decreases, and the ankle/wrist ratios increase significantly. However with drugs employed to lower the blood cholesterol concentration a significant increase in the circulation could not be demonstrated after one month of therapy, although the blood cholesterol and phospholipid levels were usually reduced. Failure to influence the circulation with such drugs may have been due to the short period of treatment or to the irreversible nature of the disease process which was present at the time treatment was started.[2]

The drugs employed were well tolerated in general. Levo-triiodothyronine in a dosage of 50 micrograms daily usually produced some weight loss and a feeling of well being. Triiodothyroacetic acid was given in a dosage of 2 mg. daily. Weight decreased slightly and the blood cholesterol level fell during the first month, but with longer periods of therapy there was a definite tendency for the cholesterol level to rise, though not to the previous value. Both of these drugs precipitated angina pectoris when given to patients with coronary artery disease. Beta-pyridyl carbinol in a dosage of 750 mg. daily lowered the blood cholesterol level fairly consistently; a dosage of 600 mg. daily lowered the level in a significant percentage of patients; but dosages below 600 mg. daily were relatively ineffective. The drug had few side-effects, probably because it was given as a long-acting, slowly released tablet. When reactions occurred they usually consisted of flushing. SC 8246 in a dosage of 15 mg. daily was generally well tolerated during the first month, but during the second month of treatment some soreness of the breasts and loss of libido occurred. Fatigability, though mild, was not uncommon. In most patients dosages lower than 15 mg. daily did not produce

[2] Many of the patients have now been followed under medical therapy for three months, and the results are unchanged.

significant lowering of blood cholesterol level. Safflower oil in emulsion form, 1 ounce twice daily, generally was well tolerated. There was a slight gain in weight. Occasionally patients with gall-bladder disease had exacerbation of gall-bladder symptoms and the emulsion had to be stopped. Corn oil, 1 ounce twice daily, was the least effective in lowering the cholesterol level, although it was well tolerated. Weight gain was slight.

SUMMARY

A method for the study of arteriosclerosis of the peripheral blood vessels is described, which consists of the simultaneous recording of pulsations from a wrist and an ankle. The assumption is made that with the development of arteriosclerosis the pulse curves of the upper extremities remain virtually unchanged while those of the lower extremities become abnormal, because the disease process usually affects the lower, but not the upper, extremities. Ankle/wrist amplitude ratios were calculated before and after arterial homografts had been placed in the aorta and iliac arteries. There was a marked increase in the ratio after surgery. No significant increase in the ratio occurred after one month's treatment with levo-triiodothyronine, triiodothyroacetic acid, beta-pyridyl carbinol, SC 8246, safflower oil emulsion or corn oil emulsion. Longer periods of therapy might have induced increases in the circulation.

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SOME ASPECTS OF HYPOTHERMIA DURING ANESTHESIA* †

HENRY W. ELLIOTT M.D., Ph.D. AND JOHN E. ADAMS M.D.

The Departments of Anesthesia, Pharmacology and Neurological Surgery, University of California Medical Center, San Francisco 22, California

The deliberate production of hypothermia has been found useful for a variety of surgical procedures. It is most valuable in operations which require reduction or cessation of blood flow to organs which have a low tolerance to ischemia. This tolerance is increased by the lowered metabolic rate of the tissues at low temperatures. In addition, there is a clinical impression that with hypothermia patients are subjected to less stress and less depression of the central nervous system by prolonged surgery. This suggests the use of hypothermia for poor-risk patients or those in whom hemorrhagic shock is a possibility. An excellent review of most aspects of hypothermia is available in a recent publication by the National Academy of Sciences-National Research Council (1).

CLINICAL OBSERVATIONS

Types of operation

Our experience with 78 patients subjected to hypothermia reflects many of the applications of this technique (Table 1). Twenty-eight cardiotomies were performed for the correction of atrial septal defects or pulmonary or aortic valve stenosis. The circulation was totally occluded for periods of two to seven and a half minutes. Repair of ventricular lesions was not attempted under hypothermia, since the required longer periods of circulatory occlusion make it advisable to use extra-corporeal circulation. Twenty-one patients were cooled for the repair of abdominal or thoracic aortic aneurysms. Aortic occlusion time ranged between thirty-four and one hundred and thirty minutes. Eighteen craniotomies were performed under hypothermia, 11 for arterial aneurysms and the remainder for vascular or highly vascularized tumors. In the patients with aneurysms, arterial inflow to the head was occluded by clamping the left carotid and subclavian and the right innominate arteries for periods of four and a half to nine minutes during the ligation or clipping of the aneurysm. The patients with brain tumors were cooled in anticipation of temporarily occluding a major cerebral artery, but this was never necessary. Six patients with partial occlusion of one or both

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The authors wish to express their appreciation to the various surgeons and anesthetists who cooperated in this project; to Doctor V. C. Sutherland for her advice and coordination of the analytical work; and to Miss Mary Abrahamsen, Mrs. Joan Bertani, Mrs. Tillie Leake and Miss Mary Lynch for their invaluable technical assistance.

TABLE 1

Type of Surgery and Ages of Patients Subjected to Induced Hypothermia

Operation	No. of Patients	Age Range (yrs.)
Cardiotomy	28	2–53
Resection of aortic aneurysm	21	43–72
Craniotomy	18	17–54
Carotid endarterectomy	6	53–63
Miscellaneous	5	2–61

carotid arteries were cooled to protect the brain against ischemia resulting from clamping the artery for endarterectomy. Occlusion times varied from five to thirty-six minutes. The remaining 5 patients included 2 with cyanotic congenital heart disease in whom shunt procedures were performed, and 1 each with esophageal varices, an occluded innominate artery, and coarctation of the aorta.

Mortality

Two fatalities occurred in the operating room. One patient had an irreversible cardiac arrest after nine hours of surgery for replacement of the thoracic and abdominal aorta. Another patient with a stenotic aortic valve suffered a progressive fall in blood pressure during manipulation of the heart with eventual irreversible ventricular fibrillation.

Two cardiac arrests were successfully treated with cardiac compression and intracardiac epinephrine. The first occurred following profound Arfonad-induced hypotension, and the second after hypotension resulting from sudden hemorrhage in a patient who had received large doses of meperidine and ataraxic drugs for twelve hours prior to surgery. Both arrests were drug-induced and not due to hypothermia.

Anesthesia

Anesthetic techniques and agents varied somewhat with the type of surgery contemplated but, in general, were chosen with the realization that less anesthesia is required at body temperatures of 28–30°C. In addition, we felt that minimal depression of the tissues by anesthetics was desirable under hypothermia because of the danger of ventricular fibrillation. Consequently, except for premedication, inhalation agents were chosen because of the ease with which the blood levels of these drugs can be altered.

After some experimentation, the following combination of agents was found satisfactory for premedication, and was administered forty-five to seventy-five minutes before induction of anesthesia. Meperidine (1–2 mg./Kg.) was given for sedation, euphoria and analgesia. It was preferred over morphine because of its shorter duration of action. Promethazine (1 mg./Kg.) was used for its long-acting antihistaminic, antiarrythmic, ataraxic and sedative properties. Atropine (0.2–0.4 mg.) was given for its parasympatholytic effects. After this medication most patients arrived in the operating room well sedated but responsive

to verbal stimuli and able to undergo smooth induction of anesthesia with cyclopropane or divinyl ether. However, the prolonged depression produced by such agents as morphine and scopolamine was notably absent, so that a greater proportion of the anesthesia was due to the inhalation agents used. We believe that promethazine provided prophylaxis against arrythmias. This impression is supported by evidence that certain antihistamines decrease both the incidence of ventricular fibrillation and the lethal temperature in hypothermic dogs (2). In addition, arrythmias in some of our patients disappeared after administration of promethazine.

In children anesthesia was usually induced by means of the open drop-technique, with divinyl ether followed by ethyl ether. After induction, an endotracheal tube was placed and ether anesthesia maintained, using a circle filter designed for infants. In adults anesthesia was induced with cyclopropane, using the closed absorption-technique and intubation with or without the aid of succinyl choline. After intubation, cyclopropane was replaced with ethyl ether, and cooling was carried out under ether anesthesia. Aside from avoiding excessive concentrations of injectable (fixed) anesthetics at low body temperatures, ether appeared to have several advantages. It permitted a high alveolar oxygen concentration and stimulated respiration, so that ventilation was adequate even at a body temperature of 26°C. Excellent muscular relaxation was provided for abdominal surgery, rapid changes in depth of anesthesia were easily accomplished, and shivering was controlled without excessive depth of anesthesia or the use of relaxants. However, when the electro-cautery unit was needed (as in neurosurgical procedures), ether was blown off after cooling and replaced with 50–75 per cent nitrous oxide. Because of the decreased (but never absent) anesthetic requirements and the increased solubility of nitrous oxide at low temperatures, this technique usually provided adequate anesthesia for surgical procedures not requiring muscular relaxation. Occasionally, small doses of d-tubocurarine were required to control shivering and it was sometimes necessary to assist respiration, although lightness of anesthesia usually compensated for the loss of the stimulant properties of ether.

Except for abdominal operations in which relaxation was required for closure, rewarming was carried out under nitrous oxide anesthesia. Moderate shivering was permitted as an aid to rewarming, and removal of ether promoted early post-anesthetic awakening.

Hypothermia

Induction of hypothermia was begun only when anesthesia was stabilized and all monitoring devices were operating. In our opinion, essential monitoring devices include the following: 1) an esophageal thermometer, since this measures the temperature of tissues near the heart, 2) direct strain-gauge blood pressure recording from either the brachial or femoral artery, 3) ECG leads from the limbs for observation of the electrical activity of the heart and early detection of arrythmias, and 4) EEG leads from the scalp to aid in determining depth of anesthesia and to ascertain loss and recovery of electrical activity of the brain

TABLE 2

Rate of Cooling in Therm-O-Rite Blanket or Ice Water

Cooling rate (°C./hr.)	No. of Patients cooled	
	Blanket	Ice water
1–2	6	—
2–3	9	—
3–4	2	1
4–5	3	10
5–6	1	13
6–7	1	12
7–8	—	11
8–9	—	5
9–10	—	2
10–11	—	2

after temporary occlusion of its blood supply. In our procedure, continuous monitoring of temperature was accomplished with a thermistor (Electro-medical Engineering Co.), and the other parameters were observed on the cathode-ray tubes of a polygraph (Electronics for Medicine, Inc.), photographic records being made when desired.

Induction of hypothermia was accomplished either in a Therm-O-Rite blanket (in which a cooling fluid circulates) or by immersion in ice water. The former method is slow and is now used only when moderate hypothermia (34°C.) is desired or when surgery can proceed during cooling as in craniotomies. The anesthetized patient is placed on the Therm-O-Rite blanket but is separated from it by wet ¾-inch thick cellulose sponges. He is then covered with wet turkish towels and surmounted by another similar blanket. Sponges and towels prevent development of pressure or thermal lesions. The whole is wrapped in wool insulating blankets and heat exchange is effected by pumping a mixture of water and propylene-glycol (2/1) at 0–2°C. through the blankets. Cooling of adults then proceeds at a rate of 1–5°C. per hour (Table 2), depending upon the bulk of the patient and the status of the peripheral circulation.

To save time, most patients were cooled in ice water and then transferred to the blanket for temperature maintenance. To facilitate the necessary movements, anesthesia was induced with the patient on a canvas sheet which can be separated longitudinally and removed from under the patient when no longer needed. When the depth of anesthesia was stabilized at plane two, the patient was lifted and placed in a tub of water at 20–22°C. When the depth of anesthesia was sufficient, this evoked no reaction and the water temperature could be lowered by the addition of ice. If signs of muscle activity appeared on the ECG or EEG tracings, anesthesia was deepened before ice was added. Children cooled rapidly at a water temperature of 15°C. but muscular or obese adults required a bath temperature of 1–5°C. to cool at a reasonable rate. As shown in Table 2, the usual cooling rate was 4–8°C. per hour. If a final temperature of 28°C. was desired, the patient was lifted out of the ice bath when the body temperature had fallen to

TABLE 3

Lowest Body Temperatures of Patients in This Series

Lowest Body Temp. (°C.)	No. of Patients
34–33	1
33–32	1
32–31	5
31–30	5
30–29	17
29–28	26
28–27	16
27–26	6
26–25	1

33–31°C. In general, the drift was less in children than in adults because of the greater surface/volume ratio; hence they could be removed from the bath at the lower temperature. However, when the circulation was impaired, drift could be excessive regardless of age or bulk. The lowest temperature reached by each patient is shown in Table 3. Approximately 75 per cent of the group were cooled to 27–30°C.

After removal from the ice bath the patients were placed on the blanket containing the circulating fluid, which had been adjusted to maintain a temperature of 28°C. The canvas sheet was removed and the patient wrapped as described previously. This permitted maintenance of temperature at 28°C. (or other desired degrees) if the operation required several hours. At the completion of the definitive surgery, the blanket temperature was raised to 40°C. for rewarming. Usually rewarming was well under way when the dressing was applied, but because of the mechanics of the heat exchanger there was a lag of about forty-five minutes before the patient began to warm. Rewarming was stopped at 34°C. because otherwise there was a tendency towards the development of an above-normal body temperature. If desired, patients could rewarm themselves spontaneously from a temperature at least as low as 31°C. without apparent ill effects.

Effects of anesthesia-hypothermia on various parameters

Under our conditions, the patients' *pulse rates* and *blood pressures* behaved approximately as reported by others (3). The pulse fell linearly with body temperature and blood pressure was well maintained under light anesthesia at the lowest temperatures attained. Pulse rates of 40–60 per minute were usual at 28–30°C., except in the presence of arrythmias or during manipulation of the heart, when rates around 100 per minute were not uncommon. Blood pressure at low temperatures proved to be sensitive to depth of anesthesia; low pressures were usually elevated towards normal by lightening the anesthesia.

A variety of *electrocardiographic changes* were observed in these patients (Table 4), although in about 44 per cent there were no abnormalities. The most common deviations from normal were disturbances of atrial conduction; there were 11

TABLE 4

Electrocardiographic Abnormalities Observed in Patients of This Series

Abnormality	No. of Cases
None	34
Shifting pacemaker	11
Atrial fibrillation	7
Atrial or ventricular extrasystoles	16
Misc. (tachycardia, nodal rhythm, etc.)	10

electrocardiograms showing p-wave alterations (shifting pacemaker) and 7 showing atrial fibrillation. Atrial or ventricular ectopic beats occurred in 16 patients, and miscellaneous abnormalities such as tachycardia or nodal rhythm developed in 10. On some occasions antiarrythmic therapy was attempted, but the results were generally unpredictable. For example, some patients with atrial fibrillation responded to digitalization but others did not. Ventricular ectopic beats frequently, but not invariably, were eliminated by intravenous administration of promethazine (25 mg.). It was not always clear whether the arrythmias were due to the anesthesia, the hypothermia or to manipulation of the cerebral or neck vessels (4); the majority were reversed as rewarming progressed.

The value of ether as a *respiratory stimulant* was exemplified by the fact that most patients breathed spontaneously at the lowest temperatures attained with no decrease in respiratory rate and only minimal decreases in tidal volume. If diminished, tidal volume could always be increased by lightening the anesthesia or if this proved undesirable, the decrease was compensated for by assisting the respiration.

Electroencephalographic changes, except during occlusion, were primarily those due to anesthesia. The tracings were most useful in helping to decide whether or not it was safe to re-occlude the circulation to the brain. All electrical activity disappeared within one minute after total circulatory occlusion and returned two to five minutes following a five-minute occlusion. When re-occlusion was necessary, it was ordinarily not performed until electrical activity had returned to the pre-occlusion level. However, in a patient in whom multiple occlusions were necessary there was a delay of thirty minutes in the return of electrical activity, and in another similar patient abnormal patterns persisted for two hours. Both patients achieved apparently normal levels of consciousness postoperatively.

Metabolic changes due to anesthesia and hypothermia varied, depending upon whether or not respiration was controlled. Either manually or artificially controlled respiration (Jefferson ventilator) tended to cause hyperventilation, which lowered blood carbon dioxide levels. Table 5 summarizes the changes in the levels of blood oxygen, carbon dioxide, lactic acid and glucose in a series of patients who breathed spontaneously during hypothermia. Arterial blood specimens obtained from the anesthetized patients before and after cooling to approximately 28°C. were used for these determinations. It is apparent that during hypothermia, the oxygen content of the blood increased and the carbon-dioxide

TABLE 5

Metabolic Changes Due to Hypothermia in Patients with Spontaneous Unassisted Respiration

Blood Levels	Normothermic	Hypothermic
pH	7.38[6]*	7.13[5]
O_2 (vol. %)	18.3[11]	20.0[11]
CO_2 (vol. %)	47.7[11]	45.0[11]
Lactic acid (mg./100 ml.)	15.4[11]	22.8[11]
Glucose (mg./100 ml.)	115.0[10]	149.0[10]

* Figures in brackets = No. of patients. All values are for arterial blood.

TABLE 6

Metabolic Changes (Blood) Due to Hypothermia and Total Circulatory Occlusion in a Representative Patient Operated on for an Atrial Septal Defect*

	pH	CO_2 (vol. %)	O_2 (vol. %)	Lactic Acid (mg./100 ml.)	Glucose (mg./100 ml.)
Normothermic	7.39	42.1	20.0	46.4	148.2
Pre-occlusion temp. = 28.9°C.	7.43	20.2	19.4	210.0	208.1
	Occlusion†				
Post-occlusion temp. = 28.9°C.	7.19	22.5	17.1	302.8	233.1
30-min. postoccl. temp. = 29.6°C.	7.36	18.6	18.7	271.2	262.0
60-min. postoccl. temp. = 30.7°C.	7.38	21.3	19.1	255.2	238.8

* Patient C.P., female, aged 13.

† Occlusion time = 5.5 minutes.

combining power decreased slightly, as might be expected in the presence of adequate ventilation and circulation and a decreased metabolic rate. Glucose and lactic acid values rose. The rise in lactic acid concentration plus a probable rise in the levels of other fixed acids probably accounts for the acidosis, which was usually indicated by the fall in pH values. Transfusions were withheld as long as practicable but in some cases may have contributed to the elevated lactic acid and glucose levels. Serum potassium, calcium, sodium and chloride levels were determined in some of the patients. The only notable change was a fall in potassium concentration from 4.3 mEq./L to 3.3 mEq./L at 28°C. in 8 cases.

Patients in whom respiration was controlled because of intrathoracic surgery presented a slightly different picture, due to induced hyperventilation. Metabolic studies on a representative patient operated on for repair of an atrial septal defect are presented in Table 6. It is apparent that blood carbon-dioxide levels were much lower. This is reflected in the rise in pH during hypothermia in spite of the high level of lactic acid before total occlusion of the circulation. As in the first series of patients, lactic acid and glucose levels increased markedly. The changes after five and a half minutes of circulatory occlusion are also shown. The pH fell by 0.24 unit, apparently due to accumulation of fixed acids, since carbon dioxide levels rose only slightly. The concentrations of both lactic acid

TABLE 7

Influence of Hypothermia, Hyperventilation and Occlusion of the Circulation on the pH of Arterial Blood of Patients Undergoing Cardiotomy

	pH	Range	No. of Patients
Normothermia	7.39	(7.30–7.52)	8
Hypothermia			
Hypothermic	7.40	(7.21–7.54)	21
Pre-hyperventilation	7.31	(7.21–7.45)	4
Hyperventilation			
After 5 mins. of hyperventilation	7.43	(7.34–7.49)	4
Occlusion			
Post-occlusion	7.24	(7.11–7.44)	21
At 30 mins. after occlusion	7.33	(7.24–7.46)	11

and glucose rose, and the return to pre-occlusion values was incomplete at sixty minutes.

In most of the patients on whom cardiotomy was performed, at least pre-occlusion and post-occlusion blood pH determinations were obtained, and these findings are summarized in Table 7. It is apparent that with ether anesthesia and controlled respiration it was difficult to raise the pH above 7.4. Four patients were subjected to extreme hyperventilation in an effort to accomplish this, with the net result of raising the pH 0.12 unit. The average fall in pH due to occlusion was 0.16 unit, with partial recovery in thirty minutes. The lowest pH recorded was 7.08 following multiple occlusions in a difficult case.

From these studies it may be concluded that ether anesthesia, induced hypothermia, and total circulatory occlusion exert profound changes on carbohydrate metabolism which result in the development of metabolic acidosis. This may be severe enough to reduce the pH to a level as low as 7.24 and in 1 case to 7.08, without apparent untoward effects.

SUMMARY

Techniques are described for premedication, anesthesia, and the induction and maintenance of hypothermia, as applied in 78 selected cases of cranial, thoracic and abdominal surgery. Complications were minimal. The principal metabolic alterations due to hypothermia were decreased carbon-dioxide production and arterial blood pH and increased levels of blood lactic acid and glucose. The alterations in pH, lactic acid and glucose were accentuated by total circulatory occlusion.

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TREATMENT OF LOW-RESISTANCE SYNDROMES* †

C. B. FAVOUR, M.D.

The Department of Immunology, Palo Alto Medical Research Foundation and the Palo Alto Medical Clinic, Palo Alto, California

The forgotten role of the host in controlling infections receives passing notice except when antibiotics fail. The purpose of this discussion is to call attention to vital host defense mechanisms which underlie recovery from all types of infectious diseases. The most important of these is the reticulo-endothelial (R-E) system made up of phagocytes, lymphoid elements and plasma cells. In Table 1 is given an outline of these cell types and their occurrence in nature.

It is interesting that below the level of vertebrates and in embryonic life in invertebrates the R-E system lacks the nonphagocytic lymphoid cells and hypersensitivity reactions, as well as plasma cells and the ability to make specific antibodies (1). These latter additions to the R-E system do much to promote the survival of the individual in a hostile microbiologic environment. As we shall see, the lymphocyte is important in virus and intracellular bacterial infection. The plasma cell is important in extracellular parasitism and antitoxic immunity.

Some of the ways in which disorders of the R-E system can bring about a low-resistance syndrome are listed in Table 3.

GRANULOCYTES

The polymorphonuclear leukocyte (PMN) is the first line of animal body cellular defense, once tissues are invaded (2). To the PMN goes the major job of ingestion and destruction of saprophytic organisms. Except when invaders are cytotoxic, they are removed from the blood stream within seconds (4, 5). Even pathogens temporarily may be cleared by the PMNs when phagocytosis once has occurred (6). For example, virulent pneumococci are destroyed by PMN if they can push them into a corner and ingest them despite their slippery capsule (7). The occasional case of pneumococcus lobar pneumonia which recovers spontaneously within two to three days before effective immunity has occurred is the clinical counterpart of this function of the PMN. It is fair to say that the promptness of recovery of a great many infections following the use of antibiotics is also due to an effective PMN response. When PMN are low or absent for one or another reason antibiotics work more slowly or may not be effective at all (8, 9).

This power of PMN to destroy micro-organisms depends on many factors. The best understood disorder of their function is reduction in their numbers. Absolute PMN counts below 1000 per cubic millimeter may increase vulnerability to secondary infections. More often counts below 500 are complicated by

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TABLE 1

Comparative Immunology of the Reticuloendothelial System

	PMN Cells	Monocytes	Lympho-cytes	Plasma Cells	Acquired Immunity	Natural Immunity
Invertebrates....	+	+	0	0	Partly specific	Variable
Vertebrates						
Embryo.....	Early	Early	Late	Late	Late	Weak
Adult.....	+	+	+	+	Specific	Present

TABLE 2

Function of Cells of the Reticuloendothelial System

PMN	Mono.	Lympho.	Plasma Cell	Tissue Cell
Phagocytosis	Granuloma formation	Hypersensitivity	Antibody formation	Natural immunity

TABLE 3

Cellular Disorders and Low-Resistance Syndromes

1. *Polymorphonuclear phagocytes* (PMN)
   - Agranulocytosis
     - Spontaneous
     - Toxic
     - Radiation exposure
   - Abnormal PMN
   - Cortisone suppression
2. *Phagocytic mononuclear cells*
   - Intrinsic difficulty in function
   - Cortisone suppression
3. *Tissue cells*
   - Intracellular pH
   - Cellular enzymes
   - Diabetes
4. *Plasma cells*
   - Deficiency in number
   - Deficiency in function
   - Deficiency in total body nutrition
   - Cortisone suppression
5. *Lymphoid system*
   - Lymphoma
   - Lymphatic leukemia

infection. On the other hand, a count of 200 per cu. mm. may be compatible with health for long periods of time.

In Table 4 is a list of various causes of leukopenia which are complicated by secondary infections.

Less well understood disorders of PMN which lead to secondary infections are those having to do with their biochemical processes. It is known, for ex-

TABLE 4

Agranulocytosis and Infection

Toxic (amidopyrine, benzol, etc.)
Infectious (infectious mononucleosis)
Blood dyscrasia (leukemia)
Radiation (ionization)
Anti-metabolites (nitrogen mustards, etc.)
Idiopathic neutropenia (? anti-cell antibodies)

ample, that the power of leukocytes to destroy micro-organisms depends in part upon their production of organic acids (10, 11), on their production of lysozyme (12–14) and on other factors such as phagocytin (15, 16). In the diabetic, lack of insulin is associated with a diminished production of lactate by the leukocytes. In this circumstance, a proper supply of insulin to the diabetic patient is a direct means of improving leukocyte metabolism and, in turn, the cell's capacity to destroy ingested micro-organisms nonspecifically. This leukocyte deficit is one of the causes of the low-resistance syndrome in the patient with unregulated diabetes.

Another instance of disordered cell metabolism leading to susceptibility to infection is deficiency of vitamin B (17) or vitamin C (17, 18). In states of low or high body temperature (19–21) and in myeloid leukemia (22) also there may be diminished phagocytosis complicated by secondary infection. In these examples of low-resistance syndromes, disordered leukocyte physiology is the primary cause for increased susceptibility to infections.

The most obvious means of treating PMN disorders (regarding either numbers or function) is to supply normal leukocytes to the host. When the cause of the metabolic deficiency can be recognized, specific treatment sometimes can be given. This is the case in diabetes or in vitamin deficiencies complicated by infection. When there is a reduction in the number of PMN, the problem is more serious. Occasionally a condition in which there is an antibody to white blood cells is complicated by neutropenia and secondary infection (23, 24). Splenectomy is helpful (24) in these patients. The removal of toxic causes of leukopenia may correct drug-induced agranulocytosis. Unfortunately there is no practical means of giving white blood cell transfusions in adequate quantities to help in an acute infectious process. Once infection is present, antibiotics are the mainstay of therapy. The wide range of antibiotic drugs now available makes it possible to control infections surprisingly well in these patients, particularly when careful bacteriologic studies are used to assure the proper choice of drugs.

MONOCYTES

The next most important R-E defensive cell is the monocyte (histiocyte). These cells are important in granuloma formation and in the conquest of intracellular infections such as typhoid and brucellosis. They are slower to appear at the site of invasion than are PMN, but are the most powerful phagocytes in the body (25). They characterize the indolent process and are able to ingest and often

to destroy agents not controlled by PMN. Efforts to show that these cells acquire immunity independent of exposure to humoral antibodies have (26) not been duplicated (27, 28). On the other hand, in some species, monocytes can destroy tubercle bacilli (29, 30) even in the absence of acquired immunity. As has been pointed out for PMN, the nonspecific destructive power of monocytes has been attributed to intracellular pH (31, 32), to organic acid production (10, 11), and to genetic factors (33). When they cannot destroy infecting organisms, as in the early phases of brucellosis or during typhoid infections (34), they may protect the infection against the destructive effects of humoral immunity or even against antibiotic treatment.

TISSUE CELLS

Although not a part of the R-E system, certain organ tissue cells have an innate capacity to block (35, 36) or to favor microbial infection. This phenomenon is akin to the nonspecific immunity of the R-E system cells.

Goodpasture (37) was one of the first to point out that before immunity or phagocytes appear in the embryonated egg, infective coliform organisms grow first in the gastro-intestinal tract, and respiratory bacteria grow first in the bronchial system. Later, Hirsch found that certain organs contain powerful natural bacterial inhibitors. For example, guinea pigs dying of experimental tuberculosis do not have renal infection. Their kidneys contain a substance called spermine (38), which in the presence of a coenzyme inhibits the growth of tubercle bacilli.

So far this knowledge about tissue immunity has not led to practical tissue-extract therapy for infections. Perhaps future research will yield valuable drugs from tissue sources. Knowledge of this type of resistance, or the lack of it, has helped to explain the relentless downhill course of many infections which have erroneously been attributed to a lack of, or to inadequate antibiotic therapy.

LYMPHOCYTES

The lymphocyte is the orphan cell of the R-E system. These cells are found packed in lymph nodes and in the spleen. They circulate in large numbers in the blood. They rapidly crowd into all types of chronic inflammatory processes, and yet little is known about their physiology.

Recent studies in which lymphoid cells have been transferred from one host to another have demonstrated 2 functions: 1) they mediate delayed-type hypersensitivity of the sort associated with allergy to chemicals, tuberculosis and viruses (39, 40); and 2) they are weak antibody producers (41, 42). Immunity to virus infection may in some way be due to an intact lymphoid system, as studies in patients with hypogammaglobulinemia have suggested (43, 44). On the other hand, suppressing the lymphoid system will diminish allergic responses of the delayed type. This has been accomplished with nitrogen mustards, ionizing radiation, and corticosteroid therapy.

Spontaneous deficits in the lymphocytes are seen in certain lymphomas. Patients with these disorders may be anergic to a variety of test agents which normally cause delayed-type reactions. They often suffer from herpes zoster and

not infrequently die of tuberculosis. Both of these conditions are caused by intracellular infections. In patients with lymphatic leukemia and lymphoma, pyogenic infections ordinarily do not develop to an unusual degree, as in patients with hypogammaglobulinemia. Upper respiratory infections are frequent, however, which is a subject which needs further study. It is only late in the course of these diseases, when other functions of the R-E systems are changed, iso-agglutinins are lost, and antibody formation is suppressed, that complex problems in pyogenic infections arise.

Treatment of infections in this type of low-resistance syndrome is most unsatisfactory. There is no specific means of managing infection in disorders of the lymphoid system. Antibiotics for pyogenic infections yield the most clear-cut results. We have tried large amounts of gamma globulin in the treatment of herpes zoster, without success. Fortunately, clinical infections are a lesser problem in this group of patients than they are in those with dyscrasias of the R-E system involving the granulocytes or the plasma cell.

HYPOGAMMAGLOBULINEMIA

Currently, the most glamorous cell of the R-E system is the plasma cell. There is clear evidence that it is the source of most antibody globulin found in the plasma (44). When this cell is absent, as in the rare syndrome of hypogammaglobulinemia, electrophoretic and immunochemical observations show a deficient capacity to form the antibodies that are important in the control of toxic and pyogenic infections. When there are disorders of the plasma cells themselves, or there are other reasons for interference with their capacity to shed antibodies into body fluids, the host is as vulnerable to certain infections as is the vertebrate embryo and the invertebrate animal, both of which lack plasma cells as well as the capacity to make antibodies.

In Table 5 is a classification of various types of low antibody-globulin syndromes (45). The dysgammaglobulinemias (46, 47) and the abnormal gammaglobulinemias are included, since persons with these disorders have a low level of *antibody* globulin and, when immunized, do not make antibody even though the serum electrophoretic studies show large amounts of protein in the gamma position.

Hypoproteinemia (48, 49) may cause secondary hypogammaglobulinemia and susceptibility to pyogenic infections. This may be due to starvation (rare) or nephrosis (uncommon), and may be present in terminal nephritis.

Treatment of hypogammaglobulinemia depends upon its cause. In the primary disease, antibiotic therapy for acute infections is satisfactory. Prophylactic substitution therapy with intramuscular injections of gamma globulin has been of value in selected and well documented cases. Less than 100 such cases have been described so far. The large amounts needed and the rarity of the disease indicate that most doctors will not have occasion to use this form of therapy. A 40-ml. dose of gamma globulin every three to four weeks is the minimal amount needed to protect an adult with hypogammaglobulinemia. This is the quantity of gamma globulin present in approximately 12 pints of blood.

TABLE 5

Low Antibody Globulin Syndromes

1. Physiologic—in infancy
2. Primary
   - Congenital—sex-linked in males
   - Acquired—adults of either sex
3. Secondary
   - Congenital panhypoproteinemia
   - Transient dysproteinemia
   - Hepatic disease
   - Nephrosis
   - Malnutrition
   - Abnormal plasma cells

The other forms of hypogammaglobulinemia are best handled by the usual measures for the control of the primary disease, and the use of antibiotics as needed. Such therapy includes antimetabolic agents and supportive measures. In this and other low-resistance syndromes, *prophylactic* antibiotic therapy is unsound in principle and inadequate or even hazardous in practice. In the hypogammaglobulinemia patients as well as in those with pyogenic infections secondary to blood dyscrasias, all infections should be treated as single episodes as they arise. There are very few circumstances in medicine in which prophylactic antibiotic treatment has been demonstrated to be of value.

CORTISONE AND SUSCEPTIBILITY TO INFECTION

Physiologic blood levels of cortisone associated with the stress of emergencies do not alter antibody production (50). Massive doses of antiphlogistic corticoids, however, will suppress antibody production (51), phagocytosis (52) and leukocyte amoeboid motion (53). In view of these known untoward effects, it is surprising how few infectious complications arise from this form of steroid treatment. Superficial saprophytic infections of the skin and mucous membranes which complicate steroid therapy are complex in origin. So are the forces in experimental infections which have indicated that mononuclear cells in cortisone-treated animals permit multiplication instead of suppression of ingested tubercle bacilli (54). In spite of these convincing laboratory findings there has been no wave of cases of active tuberculosis following the widespread use of steroid therapy now commonplace in clinical practice. If anything, the reverse situation has occurred. Instead, excessive emphasis on the infectious complications of cortisone treatment has delayed its occasional legitimate use (in combination with antimicrobial agents) to combat infections. Physiologic doses have been of value in the toxemia of typhoid (55, 56), in the shock of sepsis (57), and in certain types of tuberculosis (58). One of the results of this adjuvant treatment is the suppression of untoward allergic injury to tissue at the sites of indolent infections, which otherwise could be controlled with antibiotics and the host's own immunity. Occasionally, treatment of patients with adrenal steroids has been

complicated by serious secondary infection (59, 60). These few examples have served as just warning against the indiscriminate use of corticoids in medicine.

SUMMARY

Low-resistance syndromes are described, due to: 1) deficits in the number and function of phagocytic granulocytes, 2) disorders in the function of the lymphoid-cell system, 3) disorders in the production of antibodies by plasma cells, and 4) variations in endocrine, metabolic and genetic properties of the reticulo-endothelial system.

Treatment of low-resistance syndromes rests primarily on the use of antibiotics for specific infections. In many instances, however, a close study of the host's defense system will reveal deficits, the correction of which will aid greatly in the control of infections.

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THE USE OF RADIOISOTOPES IN A COMMUNITY HOSPITAL*

GEORGE J. CARROLL, M.D., OWEN JENKINS AND JO ANN SWAIN

Department of Pathology, Louise Obici Memorial Hospital, Suffolk, Virginia

The use of radioisotopes in hospitals is increasing, though somewhat slowly. This is particularly true in hospitals of 150–200 beds. It has been felt that in an institution of this size the use of isotopes might not be practical, and moreover the initial cost of equipment is high. Thus the idea has met with considerable resistance in some areas. In our laboratory, we thought it desirable to employ several radioisotopes for the study of various body functions. Therefore, we obtained a license to use, not only I^{131}, but also Fe^{59}, Cr^{51}, Co^{60}, P^{32}, RISA[1], and I^{131} Rose Bengal. We shall attempt briefly to present some of our methods and show how they have helped in differential diagnosis and in providing useful information for the final appraisal of the patient.

EVALUATION OF THYROID FUNCTION WITH RADIOACTIVE IODINE (I^{131})

The measurement of thyroidal radioactive iodine uptake is the mainstay of any isotope laboratory. This test depends upon the ability of the thyroid to concentrate administered I^{131}. There are several methods for testing, the easiest and most useful of which is the 24-hour uptake. Previous iodine or thyroid medication is about the only contraindication.

Normal persons and those who are typically hypothyroid or hyperthyroid present no particular problem. Frequently, however, we see patients who do not fit precisely into these categories, and in them it is occasionally necessary to run a thyroid clearance test. This measures the percentage per minute I^{131} clearance of the plasma by the thyroid gland; this percentage can be easily converted into terms of milliliters per minute. A much simpler method for the differential diagnosis of borderline cases of hyperthyroidism is the use of thyroid suppressants. After the patient is given 150 micrograms (μg.) of *l*-triiodothyronine[2] daily for seven days, the thyroidal I^{131} uptake study is repeated. Administration of *l*-triiodothyronine will reduce the uptake below 20 per cent in a normal gland, but not in a hyperfunctioning gland. The serum protein-bound iodine conversion ratio may be determined with a Squibb or Abbott Ioresin kit. This determination is based upon the fact that shortly after administration of sodium radioiodine all plasma iodine activity is in the inorganic form, but as time progresses a portion is converted by the thyroid to thyroxine, part of which is released into the blood and exists there (prior to metabolic destruction) in the form of thyroglobulin.

When a low I^{131} uptake reading is obtained, it may be desirable to differentiate

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[1] Radioiodinated serum albumin.

[2] Cytomel.

between primary and secondary hypothyroidism. In primary hypothyroidism the gland does not respond to administration of thyroid-stimulating hormone (TSH) (1), whereas in pituitary hypothyroidism the gland is in a resting state and responds to a small amount of TSH with an increase in the uptake of I^{131}. The following is an example:

A 9-year-old girl was seen because of abnormal gain in weight; the thyroidal I^{131} uptake was 15 per cent. She had been taking thyroid for one year. A thyroidal I^{131} uptake of 39 per cent was obtained following administration of 10 units of TSH. This indicated that the patient did not have primary hypothyroidism, but that the defect was probably pituitary in nature.

One should be cautious in interpreting results, however. Fibrosis with atrophy of the gland in longstanding hypothyroidism will lead to a low reading after administration of TSH. In some cases of myxedema there may be enough remaining thyroid tissue to yield a normal reading for 24-hour I^{131} uptake after administration of TSH.

BLOOD VOLUME STUDIES WITH RADIOACTIVE CHROMIUM (CR^{51})

The use of Cr^{51} for tagging red blood cells has been a great help to both our surgical and medical colleagues in performing blood volume studies (2). Sodium chromate diffuses into the cells and becomes fixed to protein. The amount of sodium radiochromate used is 35 to 50 microcuries; it is incubated with a known quantity of the patient's blood for forty-five minutes. At the end of this time, ascorbic acid (50 mg.) is added to reduce the chromium and inhibit diffusion. The material is then injected into the patient, and after twenty minutes a sample of blood is withdrawn. The blood volume can be determined quite accurately on the basis of dilution. Blood volume studies used in conjunction with electrolyte studies are of great value in clinical management. Blood can be tagged during a surgical procedure, but when the patient is a poor risk we prefer to make the first base-line determination on the day before operation. Difficulty arises in seriously bleeding patients, particularly in those with ulcer. Here the loss of Cr^{51} from bleeding distorts the blood volume picture. In these cases, RISA is the material of choice. On the other hand, in burn patients with loss of protein, Cr^{51} should be used. Only one injection is necessary with the latter, and daily volume studies can be carried out without further tagging of red cells.

The following 2 cases clearly demonstrate the value of using Cr^{51}—in Case 1 for studying postoperative fluid balance, and in Case 2 for detecting internal bleeding.

Case 1. A middle-aged white male was admitted to the hospital with beginning jaundice. Upon abdominal exploration, pancreatitis was found. The patient bled considerably during operation and his condition was poor. Therefore, during the surgical procedure, a pint of blood was tagged with radioactive chromium and administered. The results are shown in Figure 1. The first determination was made during operation; the total blood volume was 3600 ml., plasma volume 1900 ml., and red cell mass 1700 ml. During the first day the patient received 3900 ml. of fluid, and of this, 1500 ml. was whole blood; he excreted only 285 ml. of fluid. At the end of the first day, the total blood volume had increased, along with the red

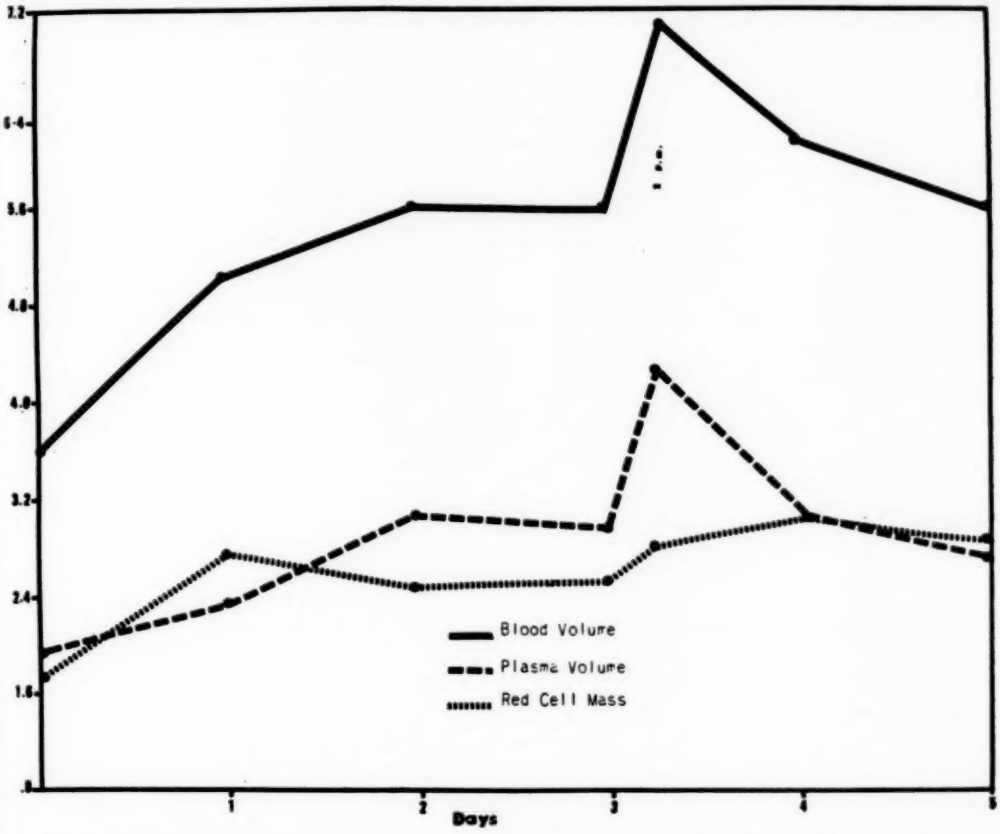

FIG. 1. Daily blood volume studies (using Cr^{51}) on a surgical patient with pancreatitis. Ordinate = blood and plasma in liters. Abscissa = length of time in days. For amounts of fluid and blood administered, and for explanation of spike in curve, see text.

cell mass. During the second day, the patient received 3000 ml. of fluid, but no blood; he excreted 1140 ml. At the end of the second day the total blood volume and plasma volume had again increased, but the red cell mass (due to dilution) had decreased. On the third day, a sudden spike in the curve was due to determination of the blood volume while the patient was receiving a pint of blood. At the end of the fourth day the proportions of plasma volume and red cell mass were approximately equal. The following day, the patient received only 1500 ml. of fluid, and the blood levels began to decline. This patient was overhydrated, but part of this was because of continuous administration of levarterenol to maintain blood pressure.

Case 2. A 9-year-old white boy was admitted to the hospital with a diagnosis of pyelonephritis. Approximately two weeks following admission he began to complain of pain in the right flank. At this time his hematocrit, which had been 36 per cent, had dropped to 24 per cent. The white blood cell count was 25,000 per cu. mm. After surgical consultation, exploration was made for what was thought to be an early abscess in the right kidney region. At operation there was extensive subcapsular hemorrhage. Blood was evacuated and the area packed. The day after operation, the morning volume of packed cells was 26 per cent and the afternoon volume was 28 per cent. In order to follow the patient more accurately, blood was tagged with radioactive chromium and administered for a blood volume determination. The following morning the volume of packed cells had dropped to 20 per cent. The patient was still acutely ill. Because of the drop in hematocrit, we took our equipment

to the patient's room, placed a probe over the right kidney, and with a scintillation counter showed that the right kidney contained twice as much radioactive material as the left kidney. The patient was again taken to the operating room, where about 2 pints of blood and clots were removed from the kidney region. As the right kidney appeared fragile and its pedicle had been torn during operation, it was removed. The kidney was hemorrhagic and near its pelvis was an area which grossly seemed to be an infarct. Microscopic sections showed an area of infarction and also glomerular changes compatible with membranous glomerulonephritis. This case demonstrates the use of radioactive chromium in the detection of internal bleeding.

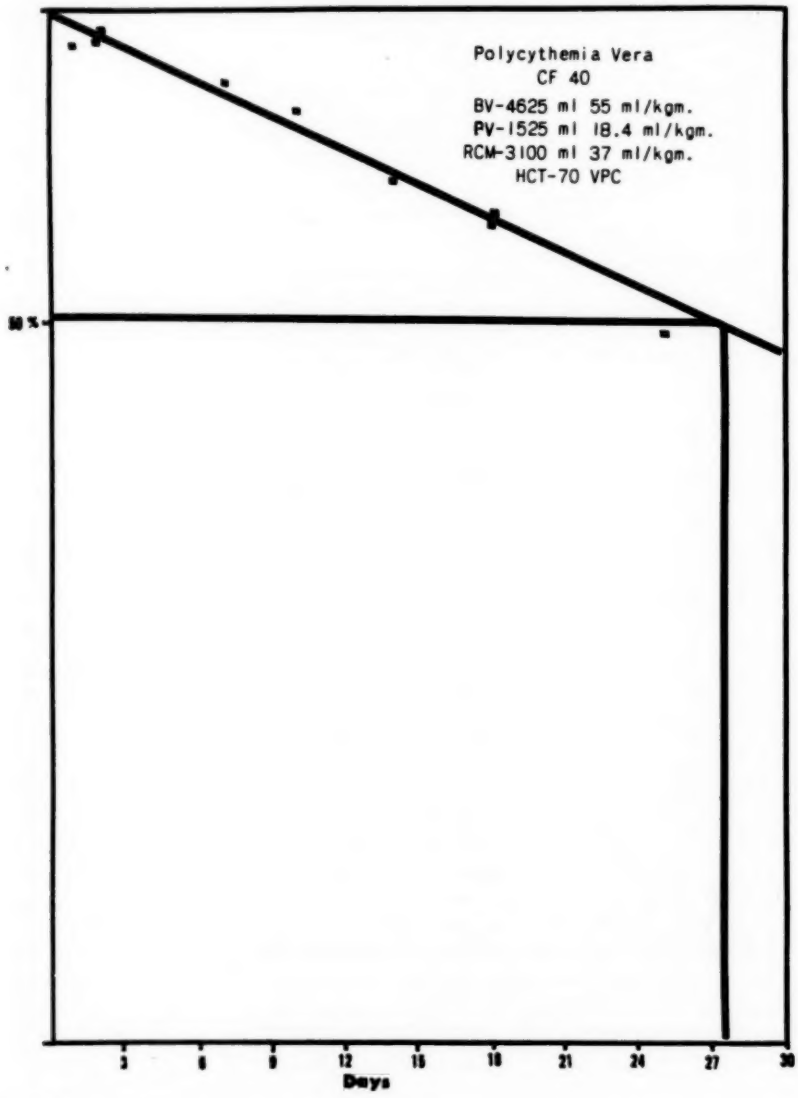

FIG. 2. Normal red-cell survival time (using Cr^{51}) in a patient with polycythemia vera. Ordinate = percentage of radioactivity remaining in blood. Abscissa = length of time in days. The half-life of the red blood cells was 27+ days.

RED-CELL SURVIVAL STUDIES WITH RADIOACTIVE CHROMIUM (Cr^{51})

Radioactive sodium chromate can also be used for red-cell survival studies. We have incorporated this method into a combined determination of blood volume and survival time by increasing the dosage of Cr^{51} (2). The tagged red cells are injected into the patient and a zero point of activity is determined in one hour. This reading represents 100 per cent activity. Normally there is a gradual decline of 1 per cent per day, on the basis of normal destruction and diffusion of chromium. The normal half-life of the red cells by this method varies from twenty-five to thirty-five days, with an average of twenty-seven to twenty-nine days. This accurate procedure will furnish essential data in estimating the degree of destruction of the red blood cells.

In Figure 2 is shown a normal red-cell survival curve for a 40-year-old colored female with hypertension and a hematocrit reading of 71 per cent. The red blood cell count varied from 7.5 to 8 million per cu. mm., and there was evidence of kidney disease. After study, a diagnosis of polycythemia vera was made. With the Cr^{51} method, the red-cell survival time was estimated to be twenty-seven days, which is normal. The patient was treated with two courses of P^{32}. At

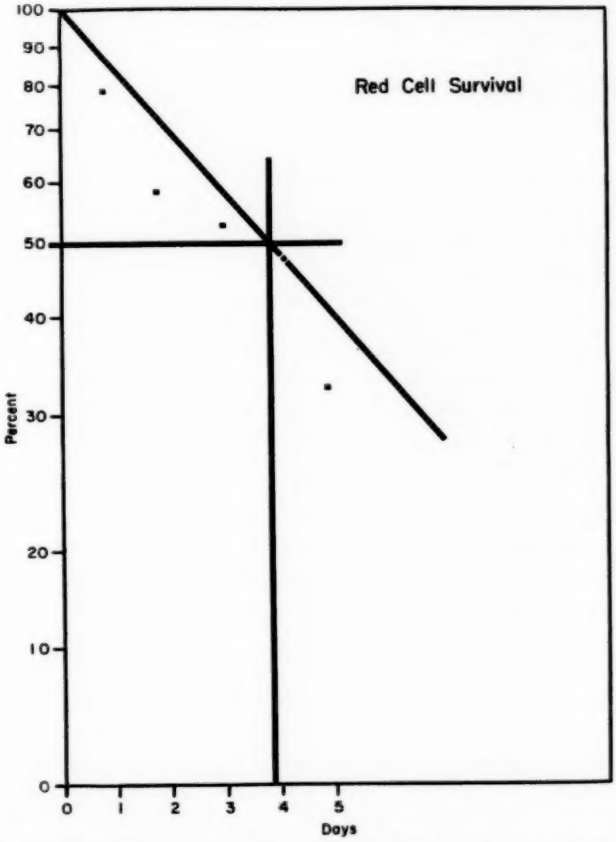

FIG. 3. Red-cell survival time (using Cr^{51}) in a patient with familial hemolytic anemia. The half-life of the red blood cells was slightly under 4 days.

present her red blood cell count is 4.5 million per cu. mm. and her blood pressure has dropped to a high-normal level.

In Figure 3 is shown a decreased red-cell survival time in a 30-year-old colored female with anemia, splenomegaly, increased fragility of the red cells without sickling (confirmed by hemoglobin electrophoretic pattern), and bilirubinemia with reticulocytosis. After study, the case was diagnosed as familial hemolytic anemia. The red-cell survival time, determined with the Cr^{51} technique, was slightly under four days. Steroid therapy was started, and had a beneficial effect. More recently, a splenectomy was performed, with excellent postoperative results.

The red-cell survival time may furnish evidence of a hemolytic process when the reticulocyte count is low and when fragility studies are inconclusive. Radioisotope studies have shown that in myeloma there is mild hemolytic anemia rather than hypoplastic bone marrow. The injection of normal Cr^{51}-tagged cells into a patient with hemolytic anemia may result in a normal value for red-cell survival time, as opposed to the survival time of the patient's own cells. This may help in the differential diagnosis of hypersplenism and aid in determining whether splenectomy will be of value in certain types of anemia.

The following case demonstrates how Cr^{51} can be used to detect gastro-intestinal bleeding.

A 49-year-old white female who had persistent anemia over a period of a year was admitted to the hospital. Six years previously she had been treated with irradiation for carcinoma of the cervix. At first the anemia was thought to be related to recurrent tumor, depression of the bone marrow from irradiation, or blood loss. The gynecologist could find no evidence of recurrent tumor. The bone marrow was hyperplastic. The results of gastro-intestinal (upper and lower) x-ray series and examination of the stools for blood were repeatedly negative. The stool examinations were sporadic, however, and a source of error as we later discovered. She was treated medically, given periodic transfusions, and was discharged. She was re-admitted to the hospital approximately six months later—again with severe anemia. A Cr^{51} red-cell survival study was made, with the thought that perhaps she had some obscure type of mild chronic hemolytic anemia which was not demonstrable by other methods. Her red-cell survival time was three days. A stool which had been sent to the laboratory (the day after the red-cell survival determination was started) to be studied for ova and parasites was noted to be black. Results of an occult blood test were positive. When the stool specimen was tested in the isotope laboratory, we found almost twice as much activity as in the morning sample of the patient's plasma. We realized that this patient must be bleeding from the intestinal tract. Apparently stool examinations for blood had been carried out during periods in which the bleeding had stopped. On the basis of the increased radioactivity in the stool, an exploratory laparotomy was performed. A small area of ulceration found in the mid ileum was resected (Fig. 5). The patient had a stormy postoperative course, but at the present time is well, with no symptoms. At operation there was no evidence of carcinoma. Apparently the ulcer was secondary to irradiation, and the abnormal red-cell survival time was due to loss of blood in the gastro-intestinal tract.

PERNICIOUS ANEMIA STUDIES WITH RADIOACTIVE COBALT (Co^{60})

A useful procedure has been developed using vitamin B_{12} tagged with radioactive cobalt (3). This is called the Schilling test and is based on the fact that vitamin B_{12} is not absorbed by patients with pernicious anemia in the absence of the intrinsic factor. When 0.5 microcurie of Co^{60}-tagged vitamin B_{12} is given

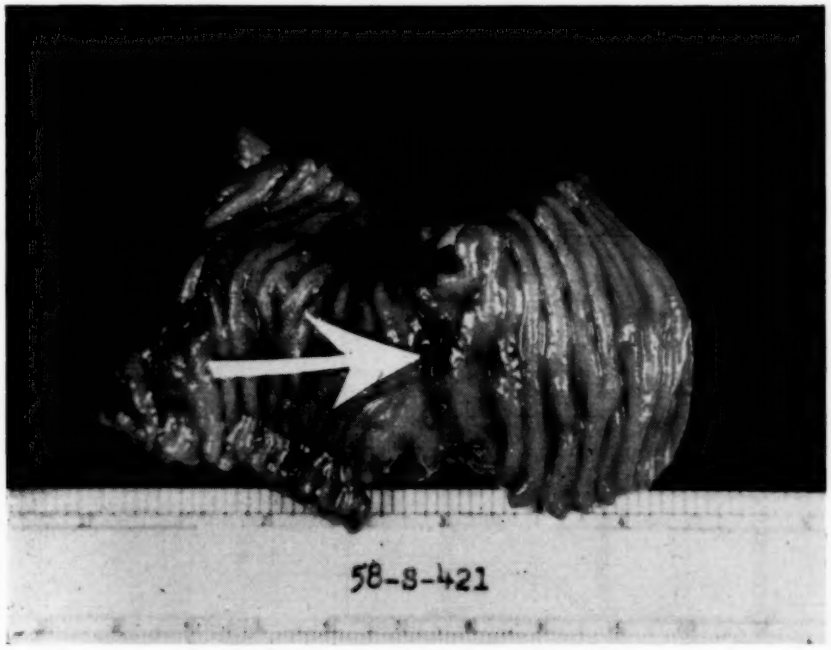

FIG. 4. Ulcer in mid-ileum in patient with gastro-intestinal bleeding, detected by examination of stool with Cr^{51}.

intramuscularly, followed in two hours by a flushing dose of 1000 micrograms of vitamin B_{12}, a normal person will excrete from 5 to 25 per cent of the radioactive material in a 24-hour urine sample. Patients with pernicious anemia excrete less than this amount, but if the test is repeated after they have been treated with intrinsic factor, the urinary excretion of radioactivity is in the normal range—as illustrated by the following case:

A 44-year-old white male complained of fatigue which had been present for one year. On admission to the hospital his red blood cell count was 720,000 per cu. mm., hemoglobin level 5.6 Gm. per 100 ml., and hematocrit 11 per cent. Examination of the peripheral blood smear revealed a macrocytic type of anemia. Gastric analysis showed no free hydrochloric acid before the injection of histamine, but the presence of acid following injection. Examination of a bone marrow smear revealed a typical megaloblastic picture. Vitamin B_{12} therapy was started. Unknown to us, folic acid was added on the fifth day. The patient was followed in the out-patient department and returned after approximately six weeks, at which time his red blood cell count had risen to 4.5 million per cu. mm. We performed the Schilling test (Fig. 5). The patient need not be in a state of remission for this test. A 24-hour urine following administration of vitamin B_{12} tagged with $cobalt^{60}$ revealed 29 per cent excretion of radioactivity. The test was repeated after intrinsic factor had been added, in order to check the determination, and the results (16 per cent excretion of radioactivity) were still within the normal range.

This case was probably not true pernicious anemia, but rather one of the other types of macrocytic anemia in which there is a megaloblastic type of bone marrow. Undoubtedly some of the cases previously diagnosed as pernicious

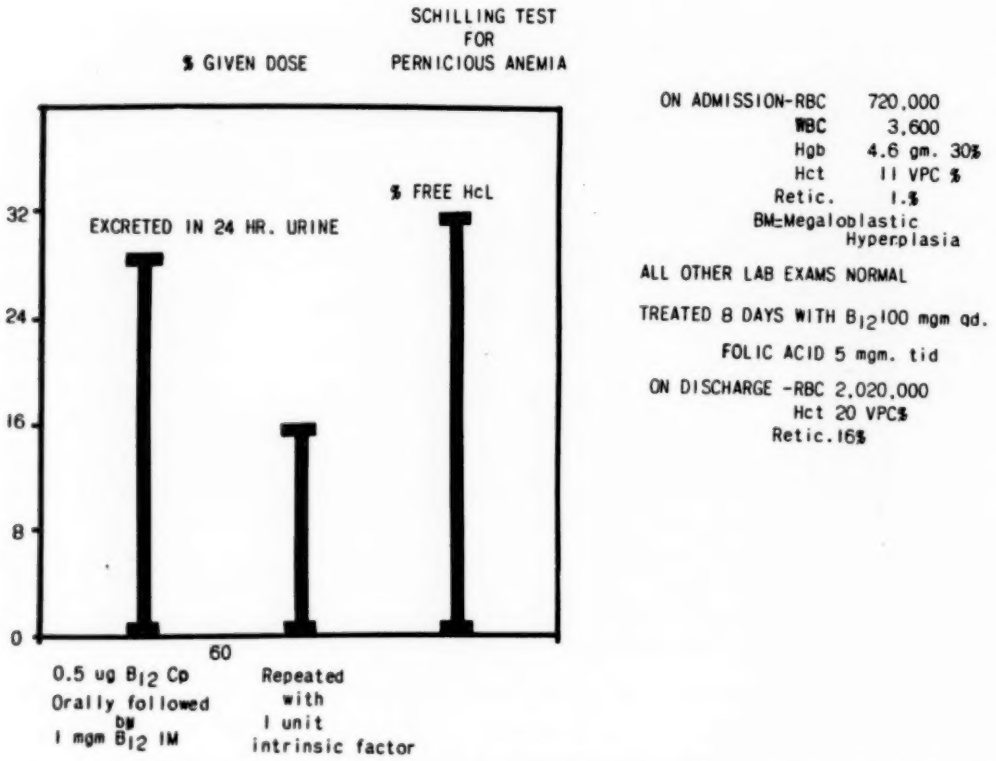

FIG. 5. Schilling test for pernicious anemia. First column represents 29 per cent urinary excretion of vitamin B_{12}-cobalt^{60} in 24 hours. Second column represents test repeated after therapy with intrinsic factor, showing 16 per cent excretion in 24 hours. Third column represents amount of free hydrochloric acid in gastric juice one hour after injection of histamine.

anemia will ultimately be removed from this category and put into such groups as gastro-intestinal malabsorption, liver disease, or (as in this case) folic-acid deficiency. The test is of great value in patients with cord dysfunction and in patients treated for pernicious anemia in whom treatment has obscured the blood picture.

DETERMINATION OF LIVER FUNCTION WITH I^{131} ROSE BENGAL

I^{131} Rose Bengal (dye) has been used to some extent in liver function tests since 1955 (4). In this procedure, a probe scintillator is focused over the liver in such a position as to avoid the gall-bladder region. A dose of 10–25 microcuries of I^{131} Rose Bengal is administered intravenously and the rate of uptake and excretion by the liver measured by a rate meter and Esterline Angus recorder. The tests appears to measure the function of the polygonal cells by measuring the hepatic uptake and excretion rates. Since only small amounts of I^{131} RB are involved, this technique can be used in the presence of biliary obstruction and also in jaundiced patients in whom the BSP test is contraindicated.

The I^{131} RB procedure seems to furnish valid information concerning liver function and circulation, as well as the patency of the biliary tract.

Normally the dye is picked up immediately and reaches a peak hepatic concentration in from ten to thirty minutes; the beginning of excretion is denoted by a well defined downward trend in the curve after forty minutes. Readings are dependent on the rate of uptake of the Rose Bengal dye, the height of the curve, and the excretion rate. We use a standard dose of 20 microcuries. In a few instances we administered Lugol's solution to diminish thyroidal pickup, but this does not seem to have any effect on the type of hepatic curve obtained. When an abnormal curve is obtained, we perform a chemical hepatogram. We have not compared the results of this test with those of the BSP test except in isolated instances.

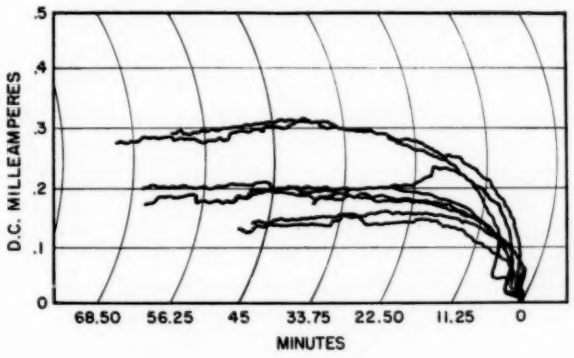

FIG. 6

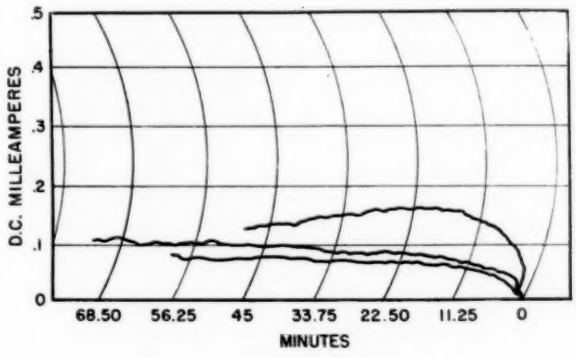

FIG. 7

FIG. 6. Composite liver function curves (I^{131} Rose Bengal) for 50 normal persons. Abscissa = minutes, reading from right to left. Ordinate = milliamperes (D.C.) on Esterline recorder.

FIG. 7. Curves denoting liver function, obtained with the use of I^{131} Rose Bengal.

Top curve (low-normal) represents a patient with subsiding Thorazine jaundice. Middle curve represents a patient with homologous serum jaundice. Bottom curve represents a patient with cirrhosis of the liver.

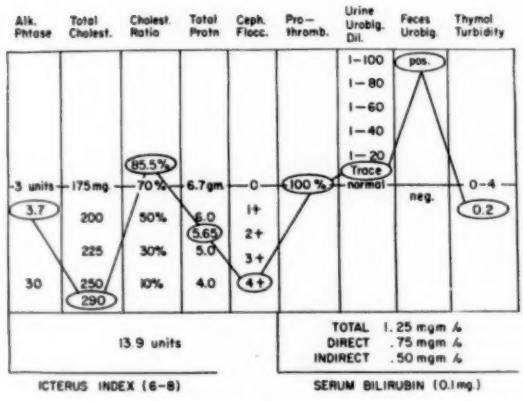

FIG. 8

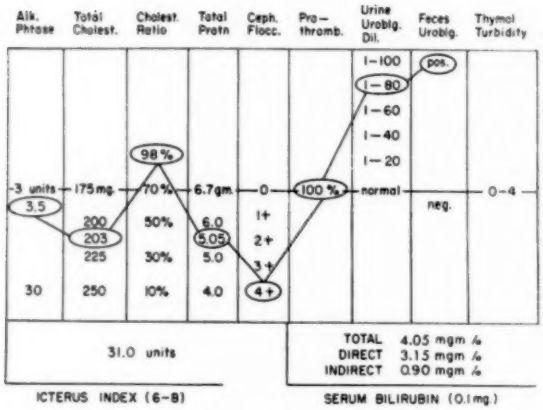

FIG. 9

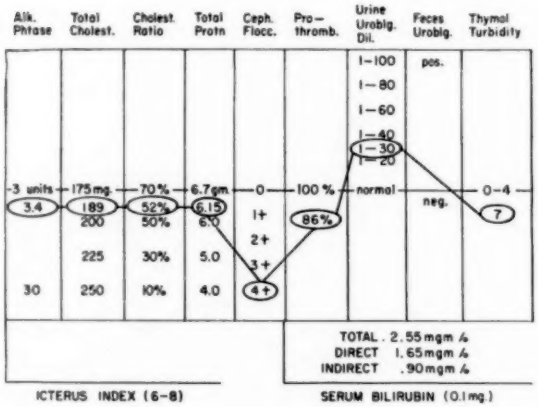

FIG. 10

FIG. 8. Chemical hepatogram on the patient with Thorazine jaundice represented in the top curve of Figure 7. Jaundice had subsided at the time the hepatogram was made.

FIG. 9. Chemical hepatogram on the patient with homologous serum jaundice represented in the middle curve of Figure 7.

FIG. 10. Chemical hepatogram on the patient with cirrhosis of the liver represented in the bottom curve of Figure 7.

Nordyke and Blahd, using 3 probes, attempted to differentiate between intra- and extrahepatic obstruction by this method (5). They placed one probe over the head, another over the liver, and the third over the lower left quadrant. Counts over the head reflected the level of the dye in the blood; over the liver, the uptake by the liver cells; and over the abdomen, the changing concentration in both the abdominal blood and intestinal lumen. Kuhl (6) took samples of blood at intervals to measure the clearance rate of I^{131} Rose Bengal from the blood. At the same time he used the head-counting method to correlate clearance rates. From a clinical point of view, in a busy laboratory, it is necessary to use the best available method that is quick, cheap, and without inconvenience to the patient. We therefore decided to use the recorder data combined with the chemical findings.

Fifty normal persons were selected to serve as controls (Fig. 6). In only 2 instances (not represented in Figure 6) did we obtain repeatedly abnormal curves. In one (male) the chemical hepatogram was normal; in the other (except for 3+ cephalin flocculation) the findings were also normal.

Three types of I^{131} Rose Bengal curves are shown in Figure 7. The uppermost curve (low-normal) is that for a patient with Thorazine jaundice. The chemical hepatogram (Fig. 8) revealed 4+ cephalin flocculation and a serum total cholesterol level of 290 mg. per 100 ml. Jaundice had subsided at the time of these chemical tests; the results of the cephalin flocculation test were negative two weeks later. In liver damage, the I^{131} Rose Bengal curve seems to become abnormal earlier and to revert to normal sooner with treatment than do the findings with other liver function tests. If this be true, it is a much more sensitive index of liver function.

The middle curve of Figure 7 is that for a 34-year-old woman with homologous serum jaundice. The I^{131} Rose Bengal uptake rate was delayed, the height of the curve was below normal, and excretion had not begun in one hour. The chemical hepatogram (Fig. 9) showed an elevated icterus index and serum bilirubin level. The concentration of total protein was slightly depressed and cephalin flocculation was 4+.

The bottom curve of Figure 7 is that for a 75-year-old man with cirrhosis of the liver. It is of the same type as that observed in hepatitis. The chemical hepatogram (Fig. 10) showed a slightly elevated serum bilirubin level, 4+ cephalin flocculation, and 7 units of thymol turbidity.

Figure 11 shows curves for 2 patients with metastatic carcinoma of the liver. The upper curve is that for a 59-year-old colored male. There is a gradually increasing uptake, and the curve is higher at the end of the designated period of one hour. The chemical hepatogram (Fig. 12) indicated an obstructive condition. Thus, in this patient, there was obstruction to the excretion of I^{131} Rose Bengal, as well as delay in the pick-up of the dye by the liver.

The lower curve in Figure 11 is that for a 62-year-old white male. The curve is flat, and similar in some respects to that observed in cirrhosis or hepatitis. A chemical hepatogram was not obtained on this patient, but cephalin flocculation and the Van den Bergh reaction were within normal limits. The picture here was abnormal, indicating some intrahepatic damage, but signs of obstruction

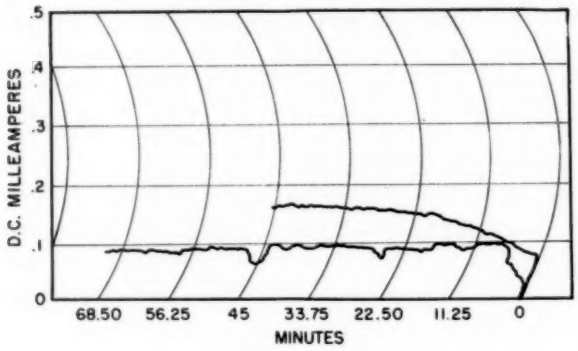

FIG. 11

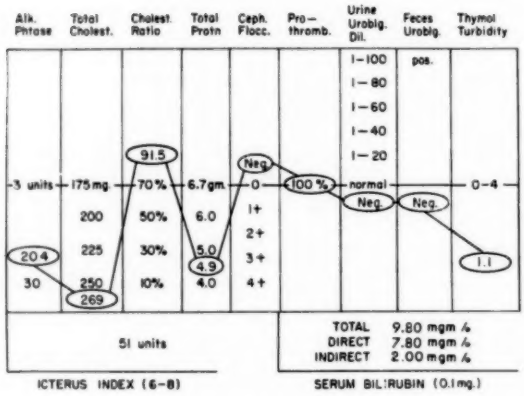

FIG. 12

FIG. 11. I^{131} Rose Bengal curves on 2 patients with metastatic carcinoma of the liver. The top curve shows a gradual increase in the uptake, with evidence of obstruction. The lower flat curve shows changes similar to those in cirrhosis and hepatitis.

FIG. 12. Chemical hepatogram on the patient with metastatic adenocarcinoma of the liver represented in the top curve of Figure 11, indicating obstruction.

were not as marked as in the other patient. Both of these cases were proved by laparotomy and biopsy.

In our experience, the I^{131} Rose Bengal test furnishes evidence of abnormal liver function. Using it with the Esterline recorder will not differentiate between intrahepatic and extrahepatic obstruction, although it may shed some light on the type of damage. Brown and Glasser concur with these findings (6). In only 2 instances did we obtain abnormal curves in otherwise normal persons, and in one of these there was a borderline result with the cephalin flocculation test. Use of the I^{131} Rose Bengal test must be guided by the time involved, the availability of radioactive material, and the simplicity of the procedure. It is our belief that it can add information to a diagnostic hepatic problem as an adjunct to other liver function tests.

SUMMARY

In a hospital of 150 to 200 beds, a radioactive isotope laboratory is a valuable addition. The clinical pathologist can utilize his existing facilities to full advantage by incorporating many of the isotope procedures into the general laboratory work. Although an isotope laboratory can be set up in other departments, or even by itself, it seems to operate to best advantage in the clinical laboratory framework.

The use of radioactive isotopes will play an increasingly important role in diagnosis and management.

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Obituaries

HAL McCLUNEY DAVISON, M.D.

1891–1958

Dr. Hal McCluney Davison was born on October 2, 1891 in Woodville, Georgia, being the youngest son of Charles Clement Davison, a well known farmer. His older brother was the late Dr. Charles C. Davison, a prominent Baptist minister. His next older brother was the late Dr. Thomas Callahan Davison, a prominent surgeon.

Dr. Davison received his elementary and high school education in Woodville, following which he attended Mercer University, being graduated in 1911 with the degrees of Bachelor of Arts and Bachelor of Pharmacy. He then matriculated at the Atlanta Medical College (now the Emory University School of Medicine), graduating with the degree of Doctor of Medicine in 1915. His internship and residency were served during the next two years at the New York Post-Graduate Hospital.

With the outbreak of World War I, Dr. Davison was sent to the United States Army Base Hospital at Camp Johnson, Florida, thence to the Presidio in California, and from there overseas to the Far East. In Siberia he served as Assistant Chief of the Medical Service in the Evacuation Hospital No. 4, American Expeditionary Forces. He received his military discharge at the end of World War I, while in Siberia.

At this time he became affiliated with the American Red Cross, serving with Herbert Hoover's Post-War Relief Commission to Middle Europe and Russia. He assumed the title and duties of Major and Deputy Commissioner of the American Red Cross, was Director of the Department of Civilian Relief, and was in charge of the Children's Boat. He organized, built and served as Chief of several hospitals, working with whichever party was in power, as this was in the midst of the Russian Revolution and Civil War. He served as Chief of the Typhus Hospital at Novonicolaevsk, Siberia in 1919 and was Chief of the General Hospital at Tomsk, Siberia in 1919 and 1920.

While in Siberia Dr. Davison became desperately ill with typhus and was cared for by a volunteer Red Cross nurse, Natalia Alexeievna Beklemisheva, a young lady from a noble Russian family. They were married in Vladivostok, Siberia, on March 31, 1920. To this union there were born three children. The daughter died at an early age. The older son, Captain Peter Hal Davison, is now serving with the United States Air Force in Berlin, and the younger son, Dr. Alexis Hal Davison, is serving his first year residency in Medicine at the University of Virginia Hospital, Charlottesville, Virginia.

Upon his return to the United States Dr. Davison completed further study in Internal Medicine at the New York Post-Graduate Hospital and in Immunology at Cornell University, working with Dr. Arthur Coca and Dr. Robert Cooke.

Dr. Davison was licensed by examination to practice medicine in the state of

Georgia in 1915. He was admitted to membership in the Fulton County Medical Society in 1921 and began the practice of medicine with his brother, Dr. T. C. Davison, in 1922.

Dr. Davison contributed abundantly in many walks of life. In medicine his early teaching career was in association with the Emory University School of Medicine and Grady Memorial Hospital. In later years he served as Chief of Medicine at the Georgia Baptist Hospital, from 1943 until retirement from this post in June 1956. He was a Diplomate of the American Board of Internal Medicine, being certified in 1937, and of the subspecialty American Board of Allergy, being certified in 1938. He was a Fellow of the American Medical Association, a life member of the American College of Physicians, and a member of the American Academy of Allergy, the American Heart Association, the Endocrine Society, the International Correspondence Club of Allergy, and the International Association of Allergologists.

He served as officer in many medical societies as well, including the American College of Allergists (Regent 1942, President 1948), The American Therapeutic Society (President 1949), the Southeastern Allergy Association (President 1946–47), the Fifth District Medical Society (President 1934), The Fulton County Medical Society (Trustee 1947–52, President 1951), the Medical Association of Georgia (President 1956–57), the Southern Medical Association (Chairman, Section on Allergy 1936), the Academy International of Medicine and Dentistry (Trustee 1948, President 1949), and American Academy of Applied Nutrition (Trustee 1948).

In 1957 Dr. Davison had conferred upon him an honorary lifetime membership in the Southern Medical Association and a special resolution was presented from the Fulton County Medical Society in May 1957 expressing profound thanks and appreciation for his dedicated service to medicine. His medical fraternity was Theta Kappa Psi.

He also belonged to the American Legion Post No. 134, the Military Order of World Wars, and the Georgia Academy of Social Sciences. He was past president of the Active Voters League, a Mason (Shriner), a member of the Atlanta Art Association, the Atlanta Civic Theater Group, the Atlanta Music Club, the Gyro Club, and Piedmont Driving Club. Dr. Davison was a member of the Druid Hills Baptist Church. His activities also included the National Conference of Christians and Jews. He was a Trustee of Mercer University and had served in the past as President and Medical Director of the General Life Insurance Company as well as President of General Securities Corporation.

Dr. Davison contributed much to medical literature with numerous publications related to his sphere of internal medicine. He spoke frequently at numerous medical meetings all over the United States. In 1955 he addressed the International Congress of Allergy at its meeting in Zurich, Switzerland.

Dr. Davison was truly one of the Men of Medicine of our day. He was courageous in his thinking, and always ready to pursue vigorously that which he considered right. He was unselfish and untiring in his efforts toward his patients, inspiring in each of them the feeling of confidence that he was interested in them

as a human being and not just as a patient. He had no prejudices against any creed, race or religion. His devotion and efforts to advance organized medicine were zealous and unflagging. He taught and practiced a philosophy of life that was and will continue to be hard to surpass.

In 1957, during his term of office as President of the Medical Association of Georgia, Dr. Davison became ill. In the spring of 1957 he entered the Georgia Baptist Hospital where the diagnosis of Hodgkin's disease was established. Despite this serious medical problem he continued the practice of medicine without complaint and died on April 26, 1958, at the age of 67 years.

With his passing we have lost an excellent physician and friend, but have gained by the privilege of having known him and served with him in the past.

C. Raymond Arp, M.D.

SEYMOUR DeWITT LUDLUM, M.D.

1876–1956

Dr. Seymour DeWitt Ludlum, a member of the American Therapeutic Society since 1926, died at his home in Gladwyne, Pennsylvania, on December 2, 1956.

Dr. Ludlum was born in Goshen, New York, August 1, 1876, the son of John Frank and Loisa May Ludlum.

He received his M.D. degree from Johns Hopkins University Medical School in 1902, and served at various hospitals in Baltimore and Philadelphia until 1912, when he established his own hospital at Gladwyne, Pennsylvania, which was known as Gladwyne Colony, for the treatment of mental and nervous diseases.

He also established and directed the Gladwyne Research Laboratory, where he spent years in research on mental disease. He authored many publications in this field.

He was Chief of Staff, Neuro-psychopathic Department, Philadelphia General Hospital, from 1910 to 1947, and since that time served as an active consultant there. He was Professor of Psychiatry, University of Pennsylvania Graduate School of Medicine, since 1914.

He was also a member of the American Psychiatric Association, American Neurological Association, American Medical Association, American Chemical Society, Association for Research in Nervous and Mental Diseases, The Philadelphia County Medical Society and Johns Hopkins Medical Society.

His only immediate survivor is a son, S. DeWitt Ludlum, Jr. who is associated in the management of the Gladwyne institution. His wife, the former Mary Mabel Stewart, died in 1954.

Oscar B. Hunter, Jr., M.D.

HAROLD GUYON TRIMBLE, M.D.

1896–1957

Dr. Harold Guyon Trimble, a member of the American Therapeutic Society, died on May 13, 1957. His untimely death at the hands of his assassin cut short an illustrious career. Dr. Trimble was born in Oakland, California, on February 27, 1896, and graduated from the University of California Medical School in 1920. His early close association with Dr. George H. Evans, a Past President of the American Therapeutic Society, helped to shape his medical career.

He was a Diplomate of the American Board of Internal Medicine and an Associate Clinical Professor of Medicine, Stanford University School of Medicine. He was a Fellow of the American College of Physicians, the American College of Chest Physicians, the American Public Health Association, and the American Geriatrics Society, and a member of the California Academy of Medicine and the California Society of Internal Medicine. He was a member of the Board of Regents of the American College of Chest Physicians and a chest specialist of international fame.

He made many trips abroad to lecture, traveling throughout Europe, South America and the Far East. On May 14, 1954, he was the recipient of the Fourth Sir Pendrill Varrier-Jones Memorial Medal, Manson House, London.

He was also the recipient of the 1957 Annual Medal of the California Tuberculosis and Health Association (for Meritorious Service in the Tuberculosis Campaign), to mention but a few of his recognitions and honors.

In 1941–42 Dr. Trimble was President of the American Trudeau Society, and in 1943–44 was Vice President of the National Tuberculosis Association. In 1941 he served as President of the California Tuberculosis and Health Association.

Dr. Trimble took an active part in community affairs and served on the Board of Directors of the United Crusade, The Salvation Army, Boys' Club of Oakland, and Bay Area Citizens' Committee for the World Health Association.

At the time of his passing, Dr. Trimble had been working on the 1958 meeting of the American Therapeutic Society in San Francisco. He had a keen interest in the affairs of the Society. Our members who were privileged to know him well found him to be a warm friend. He had splendid medical training and extensive experience, particularly in the field of chest diseases.

He is mourned by his widow, five children, and thirteen grandchildren. He was held in great affection by his family. His untimely death is a great loss to our Society.

FRANCIS M. POTTENGER, JR., M.D.

Abstracts of Current Literature

EINE NEUE METHODE ZUR PROPHYLAXE UND BEHANDLUNG DES ALTERNS MIT NOVOCAIN-STOFF H_3. (A NEW NEW METHOD IN THE PROPHYLAXIS AND TREATMENT OF AGING WITH NOVOCAINE-SUBSTANCE H_3).

Aslan, A. *Therapiewoche* (Karlsruhe) **7:** 14, 1956–57; through Excerpta Med. (Gerontol. & Geriatrics) **1:** 17 (July) 1958.

Observations made on 2,500 cases show that procaine is a substance which has a eutrophic effect on the entire organism. Clinical remissions were seen of phenomena hitherto regarded as irreversible (*e. g.*, arteriosclerosis of the brain). Lasting improvement was obtained in senile parkinsonism; hearing and certain osteo-tendinous reflexes improved. Estrogen production recommenced and various signs of aging disappeared—repigmentation of hair or new hair growth, fewer arteriosclerotic symptoms, improved CNS activity, changes in protein structure and in the albumin-globulin ratio, increased blood cholesterol level, decreased leukocyte count, stimulation of granulocyte formation, increased monocyte count, and increased globular values. An unmistakable eutrophic effect was seen in cases of atrophic ulcer, peptic ulcer, scleroderma, psoriasis, rashes, pellagra, alopecia, and vitiligo. It can be stated that procaine lowers the biologic reflection of the chronologic age to below this age.

CENTRAL NERVOUS SYSTEM STIMULATION AND SEDATION WITH DIMETHAZAN.

Batterman, R. C.; Grossman, A. J.; Leifer, P., and Mouratoff, G. J. *Am. J. M. Sc.* **236:** 162 (Aug.) 1958.

Dimethazan, which is 1,3-dimethyl-7-(2′-dimethylaminoethyl)xanthine, a new caffeine derivative, was administered intravenously in doses of 50 to 600 mg. over a two to four minute period in 66 patients with chronic diseases such as arteriosclerosis, hemiplegia, and neurologic disorders. A transitory increase in respiratory rate occurred in 77 per cent and cerebral stimulation manifested by improvement in mental status, alertness, and restlessness in 56 per cent of the subjects. In a patient markedly depressed as a result of chlorpromazine therapy, a single dose of 300 mg. of Dimethazan intravenously rapidly brought about an increase in the depth and rate of respirations and improved the patient's mental status. The central nervous system effects of Dimethazan were evaluated by administering 100 to 400 mg. three to four times daily to ambulatory patients with chronic fatigue, lack of energy, lethargy, sluggishness, listlessness, and apathy. A satisfactory stimulatory effect was noted in 68 per cent of the 84 trials. This stimulation was not accompanied by nervousness, irritability, jitteriness, or insomnia. In 47 trials, 68 per cent of the subjects had satisfactory degrees of sedation with control of an anxiety state or a hypnotic effect, or both. Transitory gastro-intestinal complaints in 4 patients and giddiness in 1 patient were the only side-actions. Complete blood counts and urine examinations showed no alterations from normal. The effectiveness of, and tolerance to Dimethazan was tested in 46 hospital patients who had generalized arteriosclerosis, hypertension, multiple sclerosis, parkinsonism, or rheumatoid arthritis and suffered senile dementia with mental depression, apathy, restlessness, or listlessness. The majority were more than 80 years of age. The drug caused no untoward reactions despite the fact that several patients had a peptic ulcer or hiatus hernia. Blood counts and urinalyses were not affected. Sixty-seven per cent of the patients showed a satisfactory clinical response with increased alertness, quietness, improvement in personality, greater cooperativeness, and less mental depression.

That Dimethazan possesses both stimulatory effects and tranquilizing action was an unusual finding. When depression was the major factor in a patient's disability, the stimulatory effect predominated. When excitability, nervousness, and anxiety were most apparent, the tranquilizing action became prominent. This combination of effects offers advantages in the control of patients with mild symptoms of depression or anxiety. The fact that stimulatory effects upon the respiratory center and cerebral function can be obtained with Dimethazan without alteration of the blood pressure and pulse rate makes the drug of value for central nervous system stimulation in geriatric patients.

ZUR TECHNIK DER PERCUTANEN HYPOPHYSENAUSSCHALTUNG DURCH RADIOAKTIVES GOLD. (THE TECHNIC OF PERCUTANEOUS HYPOPHYSECTOMY WITH RADIOACTIVE GOLD.)

Bauer, K. H., and Klar, E. *Chirurg.* **29:** 145, 1958; through Ciba Literature Review **3:** 164, 1958.

Elimination of the pituitary as a means of treatment for otherwise incurable cases of carcinoma has been accomplished by a new percutaneous technic. This method yields results as reliable as those of an operation but it is easier to carry out. Under inhalation anesthesia, the sella turcica is punctured transethmoidally and trans-sphenoidally with a hollow needle, the point of the needle being inserted about 3 to 5 mm. into the sella. The pituitary is eliminated by radiation with 20 to 40 mC. of radioactive gold (Au^{198}). Depending on the requirement, 1 to 4 gold seeds (pieces of wire) 2 to 4 mm. in length are pushed through the hollow needle and into the pituitary with the aid of a blunt mandrin. The needle is then removed. The whole process is carried out under continuous direct control with a so-called picture intensifier. Immediately afterward, two x-ray photographs are taken of the base of the skull (lateral and axial) in order to ascertain the position of the radioactive gold. The intervention lasts no longer than six to eight minutes. "Percutaneous" elimination of the pituitary was carried out on 247 occasions with favorable therapeutic results. In cases of breast cancer, success depends essentially on the level of differentiation. When the patient shows a positive response, a considerable palliative effect can be achieved with this relatively small-scale intervention.

STUDIES ON THE POSSIBLE RELATIONSHIP OF TOLBUTAMIDE TO DICUMAROL IN ANTICOAGULANT THERAPY.

Chaplin, H., Jr., and Cassell, M. *Am. J. M. Sc.* **235:** 706 (June) 1958.

Evidence in 2 patients presented, suggested that the administration of tolbutamide to patients receiving maintenance Dicumarol therapy might cause further depression of the prothrombin time to dangerously low levels. Therefore, a study was undertaken of the effects of tolbutamide on the coagulation mechanism, particularly with reference to Dicumarol therapy. The coagulation studies were designed to discover any major effects of tolbutamide on the prothrombin-thrombin and thrombin-fibrinogen stages of coagulation. Physiologic concentrations of tolbutamide in *in vitro* studies had no effect upon the coagulation of normal plasma nor on the plasma from patients receiving Dicumarol. High concentrations of tolbutamide prolonged the prothrombin time of plasma incubated at 37°C. for several hours, but this was concluded to have no clinical significance. Large doses of tolbutamide administered simultaneously with Dicumarol to rabbits produced no additive anticoagulant effect. The failure of tolbutamide to cause unusual prolongation of prothrombin time in 3 additional patients who were receiving Dicumarol lends support to the negative evidence in the anticoagulant studies reported. This lack of effect makes it appear that the "summative" anticoagulant effect observed in the first 2 patients was not related to tolbutamide therapy.

ASTERIXIS. ITS OCCURRENCE IN CHRONIC PULMONARY DISEASE, WITH A COMMENTARY ON ITS GENERAL MECHANISM

Conn, H. O. *New England J. Med.* **259:** 564 (Sept. 18) 1958.

The occurrence of the neurologic sign known as asterixis is not limited to severe liver disease and has been reported in a variety of nonhepatic disorders, the most common of which is pulmonary insufficiency with cardiac decompensation. Six additional cases of chronic pulmonary disease in patients with evidence of congestive heart failure and the occurrence of asterixis are reported. In only 1 of them did abnormalities in laboratory data suggest the presence of severe liver disease. Since liver disease could not account for the sign, an attempt was made to discover what common factor might be responsible for aterixis in the diseases in which it has been reported. Neither hyperammonemia, the hydrogen ion concentration of the blood, the carbon dioxide tension of the blood, increased intracranial pressure, abnormalities of serum electrolytes, magnesium deficiency, cerebral hypoxia, hypoglycemia, nor drug intoxication can be the primary cause. It is likely that a variety of metabolic or mechanical disturbances may interfere with the basic oxidative processes of cerebral metabolism. If this be the case, then aterixis is likely to be observed in additional diseases in which cerebral metabolism is depressed. These could include severe anemia, diabetic acidosis, hypoglycemia, barbiturate intoxication, congestive heart failure, and senility.

POLYCYTHEMIA AND RENAL CARCINOMA. REPORT OF TEN CASES, TWO WITH LONG HEMATOLOGIC REMISSION FOLLOWING NEPHRECTOMY.

Damon, A.; Holub, D. A.; Melicow, M. M., and Uson, A. C. *Am. J. Med.* **25:** 182 (Aug.) 1958.

Ten patients with polycythemia and renal carcinoma are presented and 12 previously documented cases from the literature summarized. The syndrome occurred in 4.4 per cent of 205 patients with polycythemia and 2.6 per cent of 350 patients with renal carcinoma seen in the Presbyterian Hospital (New York). The renal tumors, as well as adjacent parenchymal tissues, were not histologically unique in the 6 specimens studied. The polycythemia was, for the most part, a simple erythrocytosis without marked splenomegaly, leukocytosis or thrombocytosis. It thus resembled "secondary" rather than primary polycythemia, except that it was not dependent upon arterial oxygen unsaturation. In 2 of the patients there was complete hematologic remission following nephrectomy, for two years and for eleven years, respectively. In 2 other cases from the literature there were similar remissions for fourteen months and three years. Of the 22 patients thus far described, all 8 who underwent nephrectomy had subsequent hematologic remission, whether or not other factors may have played a part. The polycythemia can, therefore, be regarded as secondary to the renal tumor, as maintained by previous authors. A similar erythropoietic effect has been described for uterine myoma and cerebellar hemangioblastoma, as well as benign renal adenoma and several varieties of carcinoma. The mechanism for the erythrocytosis is unknown, but probably an erythropoietic substance is produced, perhaps in the tumor or in the neighboring renal parenchyma. Whatever the mechanism and its site of action, the appreciable coincidence of polycythemia and renal carcinoma makes mandatory the urologic investigation of hematuria in polycythemia. (From authors' summary. *Note:* Since completion of this manuscript, several additional cases have appeared in the literature.)

POSTURAL HYPOTENSION. VARIATIONS IN DIFFERENT DRUGS AND DIFFERENT PATIENTS.

Dern, P. L. *Circulation* **18:** 348 (Sept.) 1958.

In evaluating the magnitude of postural and nonpostural falls in blood pressure induced by ganglionic-blocking agents consideration should be given to the time spent in each

position, to correcting for postural changes that do not depend upon drug action, and to justifying the choice of control blood pressure readings. In a study of the 3 ganglionic-blocking agents, IN-292, mecamylamine and pentolinium, it was found that IN-292 produced marked falls in blood pressure in the lying position, whereas the falls in blood pressure produced by pentolinium were more dependent upon assuming the erect position. Mecamylamine had an effect intermediate between that of these two drugs. It also was observed that 1) patients who had large postural falls in blood pressure before drug action showed a tendency to small reductions in blood pressure in the erect position following administration of a ganglionic-blocking drug, but similar or larger nonpostural falls, whereas 2) patients with before-drug rises in systolic pressure (or small reductions) had large postural falls and similar or possibly smaller nonpostural falls during drug action. The explanation for the second of these observations may be that a postural rise in blood pressure in the absence of drug action represents an exaggeration of the compensatory reflex that normally maintains the blood pressure level upon assuming the erect position, and that in patients with postural hypertension there is an increase in the neurogenically maintained fraction of the blood pressure. Under these conditions, a ganglionic-blocking drug should cause a larger fall in blood pressure. In patients with postural hypotension, it may be that the neurogenic response to assuming the erect position is not sufficient to maintain the blood pressure level, so that a ganglionic-blocking drug causes a smaller fall of blood pressure because the neurogenically maintained part of the blood pressure is a smaller proportion of the whole.

RILIEVI ANATOMO-RADIOGRAFICI SULLE ARTERIE DEL BRACCIO E DELL'AVAMBRACCIO NELLE VARIE EPOCHE DELLA VITA. (ANATOMICAL AND RADIOGRAPHIC DATA ON THE ARTERIES OF THE ARM DURING THE VARIOUS EPOCHS OF LIFE.)

Donini, I.; Gaia, C., and Solbiati, G. *G. Gerontol.* (Firenze) **5:** 147, 1957; through Excerpta Med. (Gerontol. & Geriatrics) **1:** 52 (July) 1958.

A study of the arterial network of the arm and forearm at different ages has led to the conclusion that the characteristic angiographic aspects of senility begin to appear towards the age of 40 years. However, at that age the principal arteries (brachial, radial and ulnar) are still intact and these begin to show the characteristic appearance only towards the age of 60. This divergent behavior suggests that apart from the factors of senility, mechanical phenomena also have a considerable pathogenic significance. The differences between the large and the small arteries of the arm and forearm appear to be due to their different structures.

LACRIMAL HYPOSECRETION.

Elliot, A. J. *Canad. M. A. J.* **79:** 371 (Sept. 1) 1958.

Attention is called to the fact that hyposecretion of lacrimal fluid may be caused by 1) senile atrophy of the lacrimal gland, 2) Sjögren's syndrome, 3) excision of the lacrimal gland, 4) obstruction of the lacrimal ductules following burns, pemphigus or trachoma, or as the result of radium treatment of lesions near the lacrimal glands, 5) paralysis of the nerves of the lacrimal gland, as may occur in herpes of the geniculate ganglion, basal fractures of the skull, or after an operation for tic douloureux or for acoustic neuroma, and 6) intoxications such as with belladonna, or in botulism, deep anesthesia, or debilitating diseases. The absence of tears may also be a congenital defect, but this disease is rare. The literature relating to these causes and the treatment of lacrimal hyposecretion are reviewed, and personal experience with typical cases presented. Treatment in cases of senile atrophy of the lacrimal gland usually consists of a soothing alkaline eye lotion applied with an eye cup. In Sjögren's syndrome, artificial tears should be applied during waking hours. The use of gelatin and Locke's solution is preferred for this purpose, with an antibiotic or sulfonamide ophthalmic ointment at bedtime. Sealing of the lacrimal puncta is the most useful means of utilizing the tears formed by the atrophied lacrimal glands. This may be carried

out if treatment with artificial tears does not produce sufficient relief of symptoms. Both artificial tears and stenosis of the puncta have been used following excision of the lacrimal gland, in cases of obstruction of the lacrimal ductules, and in some cases of paralytic hyposecretion. Lateral tarsorrhaphy with improvement in symptoms is reported in 2 patients who sustained severe basal fractures of the skull and in whom neuroparalytic keratitis and other ocular complications subsequently developed. This operation also was carried out in one patient, along with that for tic douloureux. Other patients with operations for tic douloureux were treated by stenosis of the puncta on the affected side, with satisfactory relief of symptoms. This procedure also has been used successfully following the operation for acoustic neuroma.

SERUM TRANSAMINASE VALUES AFTER CHOLECYSTECTOMY, HYSTERECTOMY, AND OPERATIONS ON THE FRACTURED HIP.

Fisk, A. A.; Thomas R. G., and Maurukas, J. *Am. J. M. Sc.* **236:** 133 (Aug.) 1958.

Serum transaminase values were recorded at 12, 24 and 48 hours after cholecystectomy, hysterectomy, and operations on a fractured hip. Nine of 10 patients with biliary-tract operations showed a postoperative rise of more than 40 units. It was apparently not related to trauma, hepatocellular dysfunction, common-duct exploration, or preoperative obstructive jaundice. Bile contains large amounts of the enzyme, and it is, therefore, possible that handling of the biliary tract results in increased absorption of the enzyme into the vascular system. A similar rise in the level of serum transaminase was noted postoperatively in 2 of 11 patients with intertrochanteric hip fractures. Normal values persisted for 48 hours following both abdominal and vaginal hysterectomy. This test is useless in the diagnosis of myocardial infarction in a patient who has undergone cholecystectomy, must be interpreted with caution in patients with hip fracture who have undergone an operation, but is not invalidated by hysterectomy. Further study of the effects of other operations upon the test is indicated.

VERÄNDERUNGEN DER ADRENALIN- UND NORADRENALINKONZENTRATION IM MENSCHLICHEN BLUTPLASMA UNTER CHLORISONDAMIN (ECOLID). (ALTERATIONS IN THE ADRENALINE AND NORADRENALINE CONCENTRATION IN HUMAN BLOOD PLASMA UNDER THE INFLUENCE OF CHLORISONDAMINE (ECOLID).)

Giger, K. *Schweiz. med. Wchnschr.* **88:** 238, 1958; through Ciba Literature Review **3:** 204, 1958.

The effect of Ecolid on the adrenaline and noradrenaline content of human blood plasma in 15 hypertensive subjects was studied, using a fluorescent measuring method. The patients usually were given 0.5 mg. of Ecolid intravenously, whereupon the catechol amine level in the blood was determined. In general, the catechol amine concentration was found to have decreased, the effect on noradrenaline being more uniform than that on adrenaline. The catechol amines come for the most part from the adrenal medulla, although noradrenaline is also liberated from the adrenergic nerve endings. Despite the fact that the catechol amine content of the blood is very small, a certain connection between catechol amine concentration and a rise in blood pressure may be assumed, since the hormones are permanently excreted by the adrenal medulla. It is supposed that Ecolid inhibits the normal release of noradrenaline at the adrenergic nerve endings. It also is likely that Ecolid has a blocking effect even on the adrenal medulla, thus diminishing the medulla's secretion. This accounts for the reduction in noradrenaline ascertained in tests. Other experiments showed that reserpine also provokes a diminution in noradrenaline and thus likewise a fall in blood pressure. Here, however, the decrease in the noradrenaline concentration is due to a general damping down of the autonomic nervous system.

MARKED AND SUSTAINED BLOOD CHOLESTEROL LOWERING EFFECT BY MEDICATION WITH NIACIN AND PYRIDOXINE.

Goldner, M. G., and Vallan, L. E. *Am. J. M. Sc.* **236:** 341 (Sept.) 1958.

In 53 patients with hypercholesterolemia, a combination of niacin with pyridoxine produced a hypocholesterolemic effect that occurred within the first two weeks of therapy. The effective dosages were 2 to 3 Gm. of niacin and 2 to 3 mg. of pyridoxine. Pyridoxine appeared to lower the effective dose of niacin. The effect was obtained in familial as well as acquired hypercholesterolemia and in that of arteriosclerosis, uncontrolled diabetes, and myxedema. The decrease was sustained with continued therapy, and a plateau gradually reached. Twenty patients were treated for a period of ten weeks. In them the mean starting serum cholesterol level of 238 mg. per 100 ml. decreased to 203 mg. per 100 ml. When medication was interrupted, the initial hypercholesterolemia returned but a new fall could be obtained within 48 hours after resumption of the dose. A few patients could be treated effectively with approximately 2 Gm. of niacin per day. In testing smaller dosages, no response was obtained with 100 mg. of niacin per day, but small and sustained falls in serum cholesterol concentration were obtained with daily dosages of 200 mg. The most common side-effect was flushing and the feeling of warmth and lightheadedness. This was in part overcome by combining vitamin C, reserpine, and pentylenetetrazole with the vitamin preparation. Nausea and vomiting could be avoided by administering the preparation with meals. No persistent changes occurred in the peripheral circulation, the blood pressure, or the electrocardiogram. Patients with coronary disease had no recurrence of precordial pain or angina. No liver damage was demonstrated by liver function tests. No effect was noted on fasting or diurnal blood sugar levels. The mechanism of action of niacin on cholesterol metabolism is not one due to vitamin substitution therapy, but a pharmacologic effect not yet defined. (The trade name of the preparation used is Sin-Sterol.)

CALCIUM AND HORMONE THERAPY OF ESSENTIAL HYPERTENSION.

Habib, S. A. *Acta endocrinol.* **28:** 566 (Aug.) 1958.

In hypertensive patients aged 34 to 85 years, intramuscular calcium as calcium gluconogalacto-gluconate alone in 10 patients and an estrogen-androgen combination alone in 10 patients produced small but statistically significant falls in blood pressure when administered for ten weeks. When the two were combined and administered to 37 patients for ten weeks, a far more dramatic effect was obtained than with calcium or estrogen-androgen alone. A significant fall occurred in both the systolic (−32.6 mm. Hg) and diastolic (−19.7 mm. Hg) pressures. When Calcibronate replaced calcium glucono-galacto-gluconate, the fall was still significant. Except in 1 patient in whom an immediate fall in blood pressure occurred as a result of treatment, the blood pressure fell gradually in all patients. The blood pressure was followed after the cessation of treatment in 22 patients. It started to rise again within three to four weeks and after three months had returned almost to pretreatment levels. No serious side-effects occurred. Postmenopausal bleeding in 4 women did not require alterations in dosage nor cessation of therapy and disappeared spontaneously.

TESTOSTERONE TREATMENT AND 17-KETOSTEROID EXCRETION. V. ADMINISTRATION OF TESTOSTERONE PER RECTUM.

Hamburger, C. *Acta endocrinol.* **28:** 529 (Aug.) 1958.

Free testosterone applied in the form of suppositories per rectum is almost immediately absorbed. The recovery as urinary 17-ketosteroids is about 30 per cent in eight hours. This is about 60 per cent of that obtained after intramuscular injection of oily solutions of testosterone propionate. Testosterone propionate has a much slower rate of absorption from the rectum. Only an insignificant fraction of testosterone cyclopentyl-propionate is ab-

sorbed within 24 hours. When absorbed from the rectum a portion of the hormone apparently does not pass through the liver and thus avoids inactivation. This finding may have practical significance in the administration of androgens.

THE EFFECT OF INTRAMUSCULAR INJECTION OF TRYPSIN AND CHYMOTRYPSIN ON ULCERATIVE LESIONS.

Iglauer, A., and Simon, D. O. *J. Chron. Dis.* **7:** 476 (June) 1958.

Among 33 patients with ulcerative lesions of the skin treated with intramuscular trypsin, 11 had stasis ulcers, 4 had ulcers due to arteriosclerosis, 1 an ulcer due to infection, 1 an ulcer due to pressure, and 2 ulcers of unknown etiology. Thirteen patients had decubitus ulcers. One patient had an acute ulcer with slough secondary to norepinephrine therapy for shock. In 26 of the patients, the lesions had not responded to conventional therapy. Therapy was initiated for the first time in 7 patients. The usual dosage was 2.5 mg. three times daily of enzyme as crystalline trypsin in an aqueous medium, as a suspension in sesame oil, or as chymotrypsin in aqueous medium. The treatment period varied from a few weeks to two years. Sixty-four per cent of the entire group showed some improvement or healing, the result was equivocal in 15 per cent, and no improvement occurred in 21 per cent. The percentages of patients improved among those with ulcerative lesions of the lower extremities and those with decubitus ulcers were 61 and 63 per cent, respectively. In the patient with necrosis following extravasation of norepinephrine, trypsin apparently hastened separation of the slough and granulation of the wound. An inflammatory reaction at the site of injection in 1 patient subsided spontaneously. A severe generalized dermatitis occurred in another patient which probably contributed to his death from bronchopneumonia and cachexia. No evidence of plasma fibrinolytic activity was found in 4 patients in whom tests were made after single and multiple injections of trypsin. The relative therapeutic efficacies of the trypsin preparations used could not be evaluated.

DIE OSTEOMYELOSKLEROSE. BERICHT ÜBER 50 EIGENE BEOBACHTUNGEN. (OSTEOMYELOSCLEROSIS. REPORT ON OBSERVATIONS IN 50 CASES).

Klima, R.; Beyreder, J., and Rieder, H. *Wien. med. Wchnschr.* **108:** 424, 1958; through Ciba Literature Review **3:** 200, 1958.

The etiology of osteomyelosclerosis still is obscure, but chronic inflammatory conditions such as tuberculosis, articular rheumatism and exogenous bone-marrow lesions of long standing play an important part. The bone-marrow lesions include those caused by x-rays, radium, radioactive isotopes, and possibly also cytostatics. As regards pathogenesis, it is assumed from observations in 50 patients that the condition begins with a degenerative process involving bone-marrow reticulum and bone. A hyper-regenerative phase is followed by fibrosis and sclerosis of the bone marrow. Unlike aplasia of the bone marrow, in osteomyelosclerosis the hemopoietic tissue appears not to suffer primary damage. Extramedullary blood-forming centers cannot be demonstrated at first; they may become increasingly insufficient as the disease advances, with the result that the patients die of progressive anemia. In other cases, compensatory blood formation (usually of leukocytes, less often of thrombocytes as well) may "overshoot," thus leading to acute myeloblastic disorder and to a tumor-like proliferation.

EXSUDATIVE PLEURITIS IM ALTER. (EXUDATIVE PLEURISY IN OLD AGE.)

Kutschera, W., and Bosina, E. *Wien. med. Wchnschr.* **107:** 497, 1957; through Excerpta Med. **1:** 26 (July) 1958.

The theory that exudative pleurisy is mostly of a tuberculous genesis holds true only for the lower ages. In 150 patients treated in the hospital who were over 50 years of age and

showed exudative pleurisy as a primary or secondary finding, the basic disease was pneumonia (38 per cent), carcinoma (3 per cent), pulmonary infarction (12 per cent) or tuberculosis (7 per cent). Parapneumonic exudates thus are of primary importance. In carcinoma patients, males dominated with 85 per cent bronchial carcinomas. Fifty-nine patients were subjected to necropsy. Among them were 7 tubercular patients with exudative pleurisy whose basic disease always was miliary tuberculosis with dissemination in the pleura, peritoneum and pericardium. The other patients showed mainly exudative pleurisy with severe cardiac decompensation, myocardial infarction or multiple small pulmonary infarctions. So-called "rheumatic pleurisy" was not observed.

THE BARREL DEFORMITY OF THE CHEST, THE SENILE LUNG, AND OBSTRUCTIVE PULMONARY EMPHYSEMA.

Pierce, J. A., and Ebert, R. V. *Am. J. Med.* **25:** 13 (July) 1958.

A barrel deformity of the chest is said to be characteristic of senile emphysema. A study was performed to determine the relation between the barrel deformity and its associated pulmonary physiology. Measurements of the chest and physiologic studies of lung function were made in 4 groups of subjects, as follows: 1) persons 65 years of age or older with barrel deformity of the chest but without symptoms of pulmonary disease, 2) a similar group of aged persons with no deformity of the chest, 3) persons of all ages with obstructive pulmonary emphysema, and 4) healthy young subjects. The results showed with regard to aged persons that 1) obstructive pulmonary emphysema may appear from any cause and can be recognized by the presence of markedly increased resistance to expiratory air flow and a distinct abnormality in the intrapulmonary distribution of inspired gas; 2) the elastic properties of the lungs in the aged are so altered as to permit greater inflation with less negative intrathoracic pressure, which change is not usually accompanied by an increase in airway resistance; and 3) the typical barrel deformity of the chest may appear independently of any change in the lungs, or it may appear in association with emphysema. In elderly people, there is no difference in the lung compartments, total lung capacity, maximum breathing capacity, indices of intrapulmonary mixing or arterial blood gases, whether the barrel deformity of the chest be present or not. The term senile emphysema should be discarded because no physiologic evidence for senile, postural or nonobstructive emphysema is apparent.

SCLÉROSE ET VIEILLISSEMENT. LES SÉNESCENCES SANS SCLÉROSE. (SCLEROSIS AND AGING. OLD AGE WITHOUT SCLEROSIS.)

Renaud, M. *Bull. Acad. nat. méd.* (Paris) **141:** 37, 1957; through Excerpta Med. (Gerontol. & Geriatrics) **1:** 20 (July) 1958.

In spite of appearances, sclerosis does not necessarily accompany old age, and is neither a primordial, obligatory factor nor a primum movens. A report is given of 50 postmortem examinations of subjects over 80 years of age, 6 of them over 85, the oldest being 91. Of these, 27 showed important lesions of diffuse sclerosis of the valves of the left heart, of the aorta, of the large vessels and of the cerebral arteries, generally accompanied by sclerosing inflammations of the kidneys and the liver. In 23 cases, on the other hand, the vascular system was entirely normal, suggesting that the human organism may go through the classic development of senile degeneration without the slightest cardiovascular sclerosis, the latter constituting only a secondary complication provoked by accidental pathogenic factors to which aging has given rise, and favoring the appearance, aggravating the manifestations, and enhancing the consequences of all the phenomena of degeneration which constitute senescence, thereby creating the complicated and unique syndrome of late life and increasing its severity.

PLASMA TURBIDITY CHANGES AND ELECTROCARDIOGRAPHIC ALTERATIONS INDUCED BY ALIMENTARY HYPERLIPEMIA IN ANGINAL PATIENTS BEFORE AND AFTER THE ADMINISTRATION OF GASTRIC MUCIN.

Rulli, V., and Rossi, B. *Circulation* **18:** 400 (Sept.) 1958.

The hyperlipemia induced by a fat meal in patients with angina may be associated with clinical and electrocardiographic changes suggesting coronary artery insufficiency. Hyperlipemia was induced by a fat meal in 10 patients with typical long-standing angina of effort who had electrocardiographic signs of coronary artery insufficiency at rest, who had no digestive disturbances, and in whom electrocardiographic alterations developed after a fat meal. Hyperlipemia was induced by administering 200 Gm. of homogenized milk with a 40 per cent fat content. The plasma lipemia was evaluated as plasma optical density determined photometrically at hourly intervals for five hours after the fat meal. The electrocardiogram was recorded in the fasting patient at rest and every hour for five hours after the fat meal. The experiment was then repeated in the same patients, and 250 mg. of gastric mucin given along with the fat meal. Gastric mucin inhibited the alimentary hyperlipemia in all patients. Not only did the plasma optical density fail to increase after the fat meal but it diminished under the influence of gastric mucin. In 5 patients, electrocardiographic changes either did not appear or were negligible. The clearing effect of gastric mucin resembled that of heparin. It has the advantage of being active orally. Its inhibitory effect upon electrocardiographic alterations associated with a fat meal appears to be less than that of heparin.

DIE CINÉDENSIGRAPHIE, EINE PHOTOELEKTRISCHE METHODE ZUR DIFFERENTIALDIAGNOSE DES LUNGENKARZINOMS. (CINEDENSIGRAPHY, A PHOTOELECTRIC METHOD FOR THE DIFFERENTIAL DIAGNOSIS OF CARCINOMA OF THE LUNG.)

Scheer, R. *Medizinische* **7:** 422, 1958; through Ciba Literature Review **3:** 163, 1958.

Cinedensigraphy is a new photoelectric method for the early recognition and differential diagnosis of lung cancer. The kinetic status and density of the lung are ascertained by recording the so-called pulmonary capillary pulse. The technical equipment consists essentially of 2 photoelectric cells (corresponding to the 2 lungs) which can be moved in any direction and are coordinated with a conventional x-ray apparatus. The patient stands between the tube and the photoelectric cells. The latter transform the x-rays into electrical energy, which is recorded on a film. The explanation of the characteristic curves is that the density of the lung increases during systole owing to the filling of the capillaries. The converse takes place during diastole. The electrocardiogram also is recorded at the same time in order to establish the chronologic pattern of the curves. The cinedensigram is considered to be pathologic in the following instances: if the amplitude of the curve is smaller than that of the comparative curve for the other regions of the lung or is absent; if various changes in configuration are present; or if so-called mixed pulsations occur. The changes in the configuration of the curves make it possible to distinguish among various types of tumor. The value of this method for diagnostic purposes has been clearly demonstrated. In approximately 90 per cent of more than 200 patients in whom other methods of examination had yielded a negative result, the positive findings of the cinedensigram were confirmed at operation or by histologic studies.

THE CLINICAL STUDY OF QUINIDINE POLYGALACTURONATE.

Shaftel, N., and Halpern, A. *Am. J. M. Sc.* **236:** 184 (Aug.) 1958.

The absorption of quinidine polygalacturonate, a new alkaloidal salt, after oral administration resembles that of quinidine sulfate. In fasted dogs, quinidine blood levels

were observed within half an hour after the ingestion of 100 mg./Kg. Levels approximating peak values were attained within two to four hours. Quinidine polygalacturonate caused a more persistent and uniform blood concentration than did quinidine sulfate. The blood level patterns observed with therapeutic doses in human beings were roughly comparable to those observed in dogs but not as sustained, probably as a result of the larger quantities given to the animals. There were broad individual differences in the time the peak levels were reached; however, these levels were constant for each of the single doses administered (0.2 Gm. and 0.4 Gm. as quinidine base equivalent). In half of a small group of patients receiving quinidine polygalacturonate in doses of 0.2 to 0.4 Gm. four times daily, the 24-hour level (at twelve hours after the last dose) was 15 to 20 per cent below the peak value. At forty-eight hours, only traces of quinidine remained in the blood. During equivalent quinidine dosage, there were no qualitative or quantitative differences in the electrocardiographic changes produced by quinidine sulfate and quinidine polygalacturonate in man or in the dog, but in the dog, quinidine sulfate caused changes to appear earlier than did this new compound. In human beings receiving therapeutic dosages, no difference could be detected in the time of onset and the general effects of these compounds. There was no appreciable accumulation and the effects usually disappeared within forty-eight hours after the drug was discontinued. Tested in arrhythmias in patients with arteriosclerotic, hypertensive, and rheumatic heart disease, quinidine polygalacturonate proved to have the full pharmacodynamic action of quinidine in correcting disturbances in cardiac rhythm. There were no instances of gastro-intestinal distress during either rapid or chronic administration and no local irritative effects. It is pointed out, however, that when sufficiently large amounts of the drug were given, gastro-intestinal symptoms would appear. The properties of quinidine polygalacturonate should make it valuable for use in patients who have been denied the benefits of quinidine because of the occurrence of gastro-intestinal distress.

MEPHENTERMINE AND THE ARRHYTHMIAS.

Wilson, M.; Perez-Arzola, M., and Oppenheimer, M. J. *Am. J. M. Sc.* **236:** 300 (Sept.) 1958.

Mephentermine sulfate has an anti-arrhythmic effect upon the human diseased heart. This salutary action was especially noted in patients with ventricular ectopic systoles. The mechanism of action is a decrease in the refractory period, an increase in the velocity of conduction, and a positive inotropic effect. In doses up to 3 mg. per kilogram administered intravenously, there was no significant electrocardiographic effect in patients with chronic atrial fibrillation. Effective reduction in functional atrioventricular block was produced. Supraventricular tachycardia with second degree atrioventricular block represents a contraindication to the use of mephentermine. The antifibrillatory properties of mephentermine may be of value in open heart surgery with therapeutic cardiac arrest. Theoretically, an oral preparation of mephentermine may find use as an adjuvant to digitalis in patients with chronic congestive heart failure (Authors' summary).

NEWS AND NOTICES

WANTED: OLD PHOTOS OF PHYSICIANS DRIVING ANCIENT CARS

The Illinois State Medical Society is preparing an exhibit centered around an Illinois Medical Journal article which told of the role of physicians in the development of the automobile in the United States at the turn of the century.

To help illustrate this exhibit, the Society will appreciate the loan of old photographs showing physicians at the wheels of cars of 1900–1910 vintage. Scenes showing difficulties on the road, or poor highway conditions, are especially desired. Enlargements will be made of these photographs and the originals returned undamaged.

Photographs should be accompanied by a memo giving the name and town of the physician, whether living or deceased, and the make and year of the automobile. They should be sent to Mr. John A. Mirt, Illinois State Medical Society, 185 North Wabash Avenue, Chicago 1, Illinois.